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Measurement of Effective Renal Plasma Flow in Man by External Counting Methods[1]

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The use of single injection clearance methods has become increasingly popular with the availability of radioisotopes for studying renal function (1,2,3). Equations derived from an open two compartment model (4) yield accurate results when comparing clearances calculated from the disappearance of Ortho-iodohippurate ^{131}I (OIH ^{131}I) from the plasma with standard Para-Amino-Hippurate (PAH) clearances. Several authors have attempted to further simplify the procedure by reducing the number of plasma samples used. However, these methods (5,6) result in a loss of accuracy which makes them unsuitable in many situations. There are several theoretical and practical advantages to be derived from external counting techniques when using OIH ^{131}I. External monitoring is comparatively simple. It is possible to mathematically reconstruct the entire plasma disappearance curve from only two plasma samples and to calculate the renal clearances with the same accuracy as the entire plasma curve. Since the curve obtained is continuous, it offers an unlimited number of points to plot and sampling errors are avoided. Collection of urine continues to be unnecessary and the physician can easily perform two clearances simultaneously on two patients. This report describes a method for calculating effective renal plasma flow by external counting methods.

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EXPERIMENTAL METHODS

Nineteen subjects with varying degrees of renal function were studied; eighteen patients were placed supine and an indwelling urethral catheter was inserted in the bladder. PAH clearances were performed by standard techniques with 30 minute collection periods (7). A Riley needle was placed in a vein in the arm opposite the PAH infusion and in twelve patients a 2 × 2 inch NaI (Tl) scintillation crystal and photomultiplier tube with 3.3 inches of lead collimation (3-inch bore) was aimed at the zygomatic arch of the skull touching the skin. At the beginning of the first clearance period (45 minutes after the priming dose of PAH), a single injection of 75μC of OIH ^{131}I was given intravenously. The radioactivity over the head was continuously recorded on magnetic tape with a Picker dual digital rate computer. The dose syringe was weighed before and after the injection. Blood samples were withdrawn at five-minute and then at ten-minute intervals for 90 minutes. A syringe containing 12.5μC of OIH ^{131}I was used as an aliquot for the dose which was made up to volume after injection into a 500 ml flask. The aliquot syringe was weighed before and after injection into the flask. One ml of each plasma sample was counted in a NaI (Tl) well-type

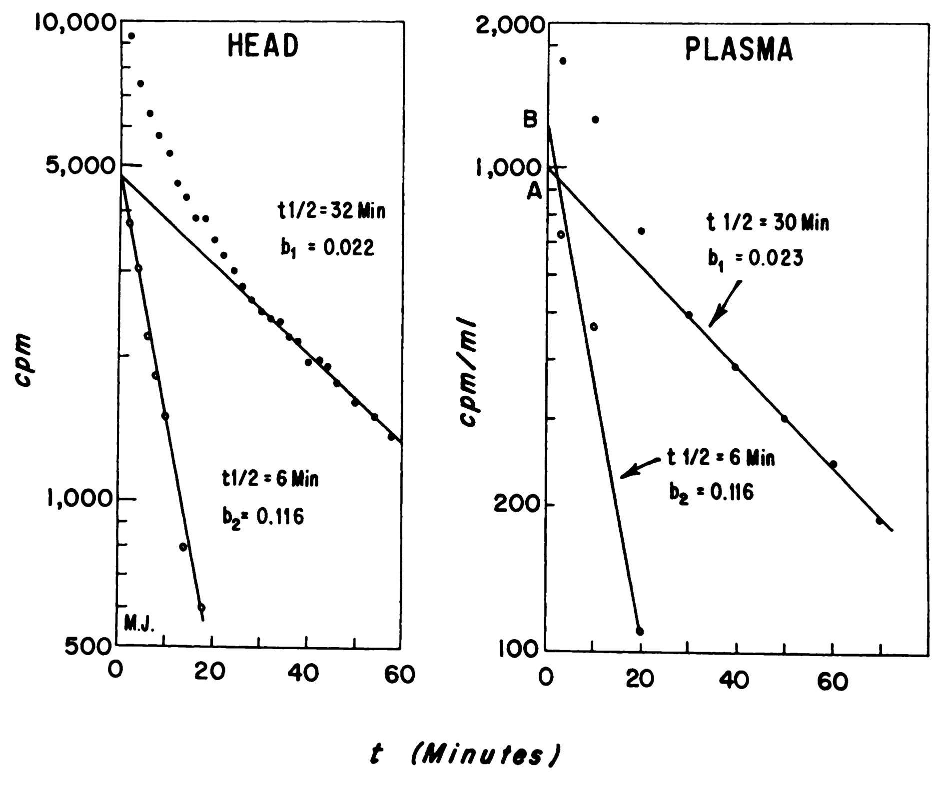

Fig. 1. The curve obtained by external monitoring over the head is on the left. On the right is a plasma curve obtained simultaneously in the same subject. The relative intercepts of the two curves differ, but the slopes of the components are similar. The actual values of the slopes for twelve patients are given in Table I.

scintillation counter. The amount of radioactivity in each plasma sample was plotted on semilogarithmic graph paper as cpm per ml against time. The curves obtained by counting over the head were plotted on semi-logarithmic graph paper as cpm against time. The remaining subject was anephric and PAH clearances were not done. All shipments of ortho-iodohippurate were chromatographed for free ^{131}I (8); none contained more than 1% free iodide.

ANALYTICAL METHODS

The plasma disappearance curves could be described by two components satisfying the equation $X = Ae^{-b_1t} + Be^{-b_2t}$ where:

X = concentration of isotope at time t

A = time zero intercept of slow component with slope b_1

B = time zero intercept of fast component with slope b_2

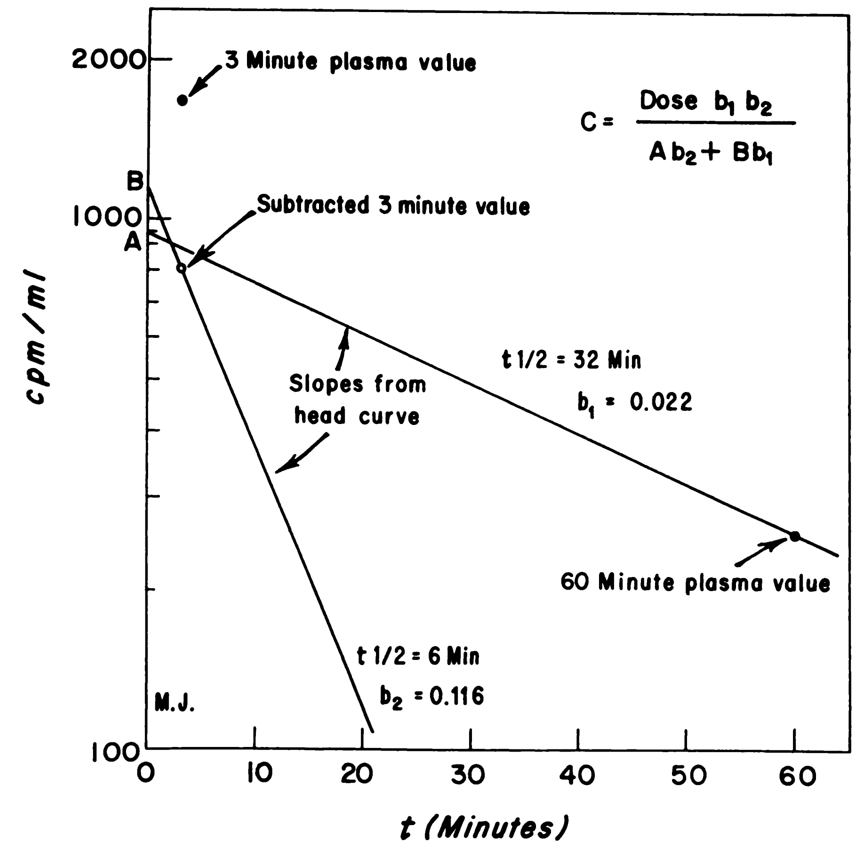

Fig. 2. Method for reconstructing the plasma curve. The 60-minute plasma value (Cpm/ml) is graphed and a line with the slope of the terminal component (b_1) of the external head curve drawn to pass through it. The three- or five-minute plasma value is graphed and the three- or five-minute value of the terminal component subtracted. A line with slope b_2 is calculated from the external head curve and is drawn through the resultant value and the plasma curve is reconstructed.

This type of curve may be obtained experimentally from an open two-compartment system where the dose is injected into the first compartment, equilibrates with a second compartment and is excreted from the first compartment via the kidney. This model has been utilized by Sapirstein (4), Bianchi (2), Blaufox (9) and others and may be used to calculate renal clearance by the equation $C = \frac{Db_1b_2}{Ab_2 + Bb_1}$ where: C = the renal clearance and D = the injected dose. The derivation of this equation may be found in the report of Sapirstein (4) and the modified notation is reported by Blaufox (1).

The disappearance curve obtained in each patient by counting over the head appeared to be composed of the same components as the plasma curve (Figure 1). However, the relative intercepts at time zero were different. The level of the time zero intercept was adjusted to correspond with the plasma curve by using two plasma samples as shown in Figure two. The plasma level at 60 minutes was plotted on semi-logarithmic graph paper and a line with slope b_1

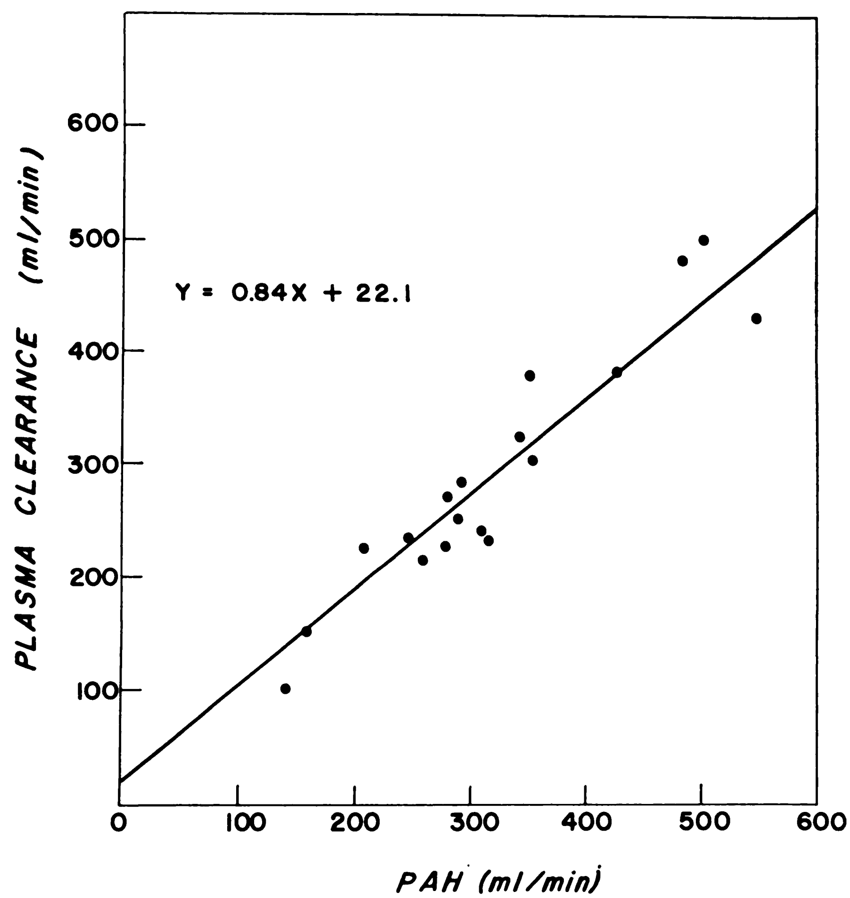

Fig. 3. Correlation of plasma clearance of Orthoiodohippurate ^{131}I and standard PAH clearances performed simultaneously.

drawn through it. The plasma value at three or five minutes was then plotted. If the value of the line with slope b_1 at three or five minutes is subtracted from the three or five minute plasma value, the resultant value is intercepted by the early component (b_2). A line with slope b_2 is drawn through the resultant three or five-minute value and the plasma curve can be reconstructed by the addition of these two lines (Table 1). The values for A and B thus obtained may be used to calculate the clearance.

RESULTS

The renal clearance of Orthoiodohippurate ^{131}I was calculated from complete plasma disappearance curves using the above equation. The ratio of plasma OIH clearance divided by the simultaneously performed PAH clearance was 0.91. The correlation coefficient for 18 simultaneous plasma OIH and PAH (Figure 3) clearances was 0.88 ($p < .01$) with a regression coefficient, 0.84. In twelve patients (Figure 4), the external head clearance calculated as described above divided by PAH was 0.97, where the correlation coefficient was 0.89 ($p < .01$) with a regression coefficient of 0.97. The external head clearance divided by the

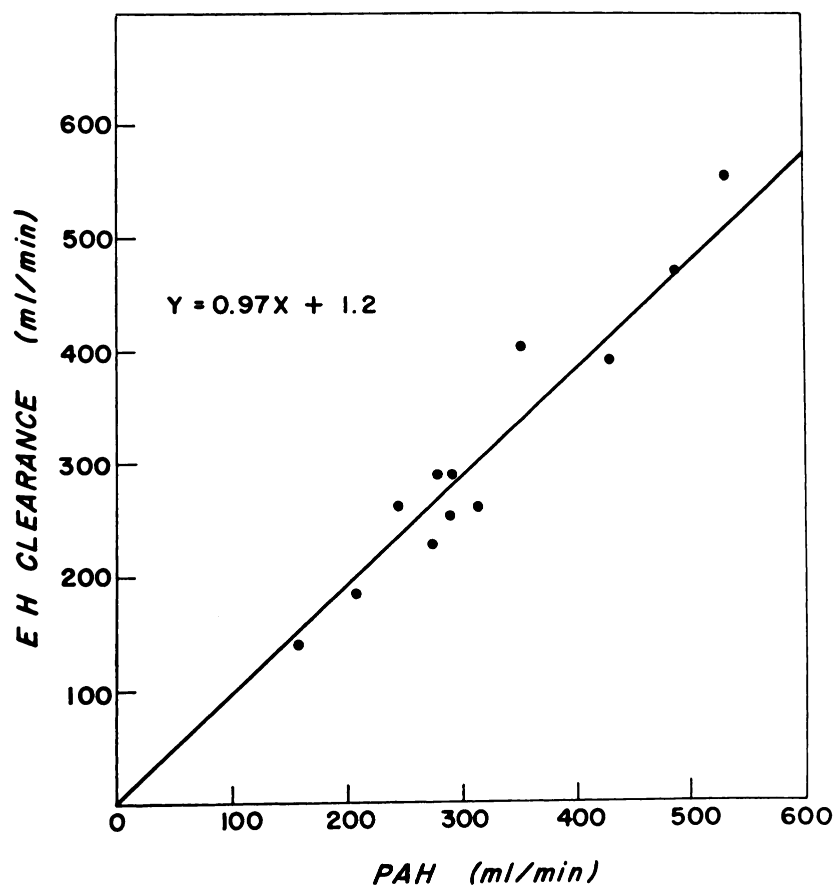

Fig. 4. Correlation of external head clearance and simultaneous standard PAH clearance.

plasma OIH was 1.04 with a correlation coefficient (Figure 5) of 0.90 ($p<.01$) and a regression coefficient of 0.86. The values for the external head clearance and the plasma OIH clearance were not significantly different ($0.40<p<0.50$) by the t test. All three methods correlated with each other closely. The results are tabulated in Table I, II, and III.

DISCUSSION

The results obtained in this study confirm the correlation between single injection plasma clearances of OIH ^{131}I and standard PAH clearances. The ratio of 0.91 of OIH/PAH is identical with that reported by Burbank and associates (8), using simultaneous continuous infusions of OIH ^{131}I and PAH. It has been suggested that the slightly lower clearance of OIH ^{131}I may be explained by the fact that trace doses may not be as completely extracted by the kidney. Bianchi (2) has shown that adding carrier OIH will raise isotopic clearances to levels more closely comparable with PAH.

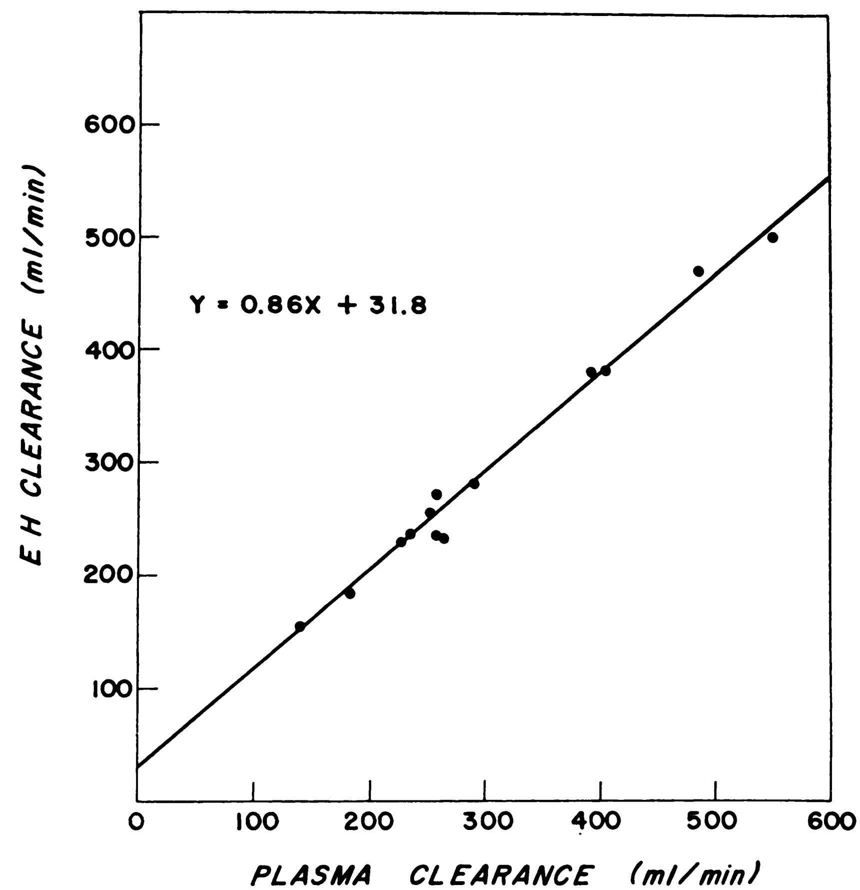

Fig. 5. Correlation of external head clearances and simultaneous plasma clearances of Orthoiodohippurate ^{131}I.

The use of external counting to determine ERPF has also been suggested by Bianchi (2). This method offers several advantages over the plasma curve. There is less frequent blood sampling and continuous recording of the curve permits more accurate analysis of the slopes by affording more points for graphing. There are, however, disadvantages, chief of which is the problem of geometry and errors introduced by the possibility of the patient moving. However, the simplicity of the method offers a quantitative approach to measuring effective renal plasma flow during the performance of a radioisotope renogram or as a routine procedure in any hospital with a radioisotope unit. It is not necessary to perform the test beyond 60 minutes to obtain an accurate estimate of the components of the curves.

The disadvantages of such an approach are the potential sources of error. These include changing extraction ratios or changes in ERPF and renal blood flow during a recording which introduces an error throughout the test. These difficulties apply to all methods of measuring ERPF. Changes in blood volume or the accumulation of edema fluid will introduce errors in the volume of distribution which will make the single injection clearance calculations inaccurate. The substance used for the test must be excreted only by the kidney. This method will yield a value for clearance even in patients with no renal function. This value is less than 30 ml/min and may be attributed to continuing distribution of OIH ^{131}I in body fluids and a small amount of biliary excretion in the absence of renal function. In these cases, the term plasma disappearance is preferable to clearance. Excretion by other organs cannot be differentiated from

TABLE I

Patient	*A(cpm/ml)*		*B(cpm/ml)*		$b_1(min^{-1})$		$b_2(min^{-1})$	
	E.H.	*P.*	*E.H.*	*P.*	*E.H.*	*P.*	*E.H.*	*P.*
1	1200	2000	3800	2500	.025	.029	.173	.139
2	2100	2200	3195	1950	.017	.017	.231	.077
3	980	1000	1000	1250	.022	.023	.116	.116
4	1650	2500	5200	4500	.024	.032	.231	.231
5	820	670	1800	1750	.024	.022	.116	.099
6	2000	2400	3700	3700	.015	.018	.116	.099
7	2350	2350	3600	3600	.019	.019	.087	.087
8	3000	3000	4200	4200	.019	.019	.116	.116
9	2050	2275	2800	3100	.020	.020	.099	.116
10	1250	1400	1600	1400	.016	.016	.139	.116
11	3400	3400	2200	2300	.020	.020	.116	.139
12	2900	3700	3050	3300	.012	.016	.077	.139

Values obtained from 12 simultaneous external head and plasma curves. A, B, b_1 and b_2 are defined in the text. E.H. is the value based on the external head curve and P is the value obtained from the plasma curve. A and B for E.H. are calculated as described. The patient numbers correspond to Table III.

renal excretion. Since the plasma is sampled only twice, accuracy in timing and pipetting is critical. If this test proves popular, the development of a helmet type recorder which can be placed on the patient's head can resolve the problems of geometry and movement. Although blood sampling is still necessary, it is conceivable that further technical progress will permit calibration of external recording instruments without sampling of blood.

SUMMARY

A method has been devised to measure accurately the effective renal plasma flow (ERPF) in man by external counting over the head after a single injection of Orthoiodohippurate ^{131}I. The external head curve is calibrated with two plasma samples drawn at three or five minutes and sixty minutes. The clearance is calculated from the slopes and intercepts of the components of the corrected curve as plotted on semilogarithmic graph paper. This method correlates closely with clearance calculated from continuous infusions of PAH ($r=0.89$). The previously reported correlation of plasma OIH clearances and PAH clearance is confirmed. External counting offers a means of determining renal function accurately without urine collection or multiple venepunctures.

TABLE II

Patient	*ml/min*			*% Difference*
	**OIH*	*+PAH*	*Difference*	
1	430	546	−116	21.24
2	501	502	− 1	.02
3	481	482	− 1	.02
4	382	427	− 45	10.54
5	304	352	− 48	13.64
6	378	352	+ 26	7.39
7	324	340	− 16	4.71
8	233	312	− 79	25.32
9	240	308	− 68	22.08
10	282	291	− 9	3.09
11	253	287	− 34	11.85
12	227	273	− 46	16.85
13	269	277	− 8	2.89
14	215	258	− 43	16.67
15	234	246	− 12	4.88
16	225	206	+ 19	9.22
17	153	159	− 6	3.77
18	100	137	− 37	27.00

*Values derived from analysis of a two component plasma disappearance curve. The disappearance of Orthoiodohippurate ^{131}I in an anephric man yielded a value of 29 ml/min.

+Standard continuous infusion clearances.

TABLE III

Patient	ml/min			% Difference
	+PAH	*Head	Difference	
1	546	550	+ 4	.73
2	482	468	−14	2.90
3	427	392	−35	8.19
4	352	404	+52	14.77
5	312	261	−51	16.35
6	291	291	0	0
7	287	253	−34	11.85
8	273	227	−46	16.85
9	277	290	+13	4.69
10	246	258	+12	4.88
11	206	181	−25	12.14
12	159	139	−20	12.58

*Values derived from analysis of a two compartment curve obtained by external counting over the head. Two plasma samples were used as described in the text to calibrate the curve. The disappearance of Orthoiodohippurate ^{131}I in an anephric man calculated from the head curve was 15 ml/min.

+Standard continuous infusion clearances.

REFERENCES

1. BLAUFOX, M. D., SANDERSON, D., TAUXE, W., WAKIM, K., ORVIS, A., AND OWEN, C. A., JR.: Plasmatic Diatrizoate-^{131}I Disappearance and Glomerular Filtration in the Dog, *Am. J. Physiol.*, **204**:536, 1963.

2. BIANCHI, C., AND TONI, P.: Possibilita Di Impiego Dello O-Iodo-Ippurato Di Sodio (Hippuran) Marcato Con^{131}I, Per La Valutazione Della Portata Renale Plasmatica, *Minerva Nuc.*, **6**:34, 1962.

3. WAGNER, R., TAUXE, W., MAHER, F., AND HUNT, J.: Measurement of Effective Renal Plasma Flow with Sodium Iodo-Hippurate ^{131}I, *J.A.M.A.* **187**:811, 1965.

4. SAPIRSTEIN, L. A., VIDT, D., MANDEL, M., AND HANUSEK, G.: Volumes of Distribution and Clearances of Intravenously Injected Creatinine in the Dog, *Am. J. Physiol.*, **181**:330, 1955.

5. BLAUFOX, M. D., FROHMULLER, H., CAMPBELL, J., UTZ, D., ORVIS, A., AND OWEN, C. A., JR.: A Simplified Method of Estimating Renal Function with Iodohippurate ^{131}I, *J.S.R.*, **3**:122, 1963.

6. BRIGGS, J., AND BOYLE, J.: Measurement of the Fall in the Level of Plasma Radioactivity After Intravenous Administration of Radiohippuran as A Test of Renal Function, *J. Clin. Path.*, **18**:369, 1965.

7. SMITH, H., FINKELSTEIN, N., ALUMINOSA, L., CRAWFORD, B., AND GRABER, M.: The Renal Clearance of Substituted Hippuric Acid Deriviatives and Other Aromatic Acids in Dog and Man, *J. Clin. Invest.*, **24**:388, 1945.

8. BURBANK, M., TAUXE, W., MAHER, F., AND HUNT, J.: Evaluation of Radioiodinated Hippuran for the Estimation of Renal Plasma Flow, Proc. Staff Meeting, Mayo Clinic, **36**:372, 1961.

9. BLAUFOX, M., ORVIS, A. L., AND OWEN, C. A., JR.: Compartment Analysis of the Radiorenogram and Distribution of Hippuran I-131 in Dogs, *Am. J. Physiol.*, **204**:1059, 1963.