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The Quantitation of the Renografin-Iodine-131 Renogram for Renal Clearance Determination[1]

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A great deal of clinical experience and body of experimental data are now available in relation to the ortho-iodo-hippuric (^{131}I) acid renogram. Numerous efforts have been attempted to quantitate renal clearance by the utilization of ortho-iodo-hippuric (^{131}I) acid renograms. These, for the most part, have been of no avail. This has prompted Winters to make the statement that the quantitative analysis of the radioisotopic renogram is not "dependable" (6).

The purpose of this paper is to present our experience with the Renografin (^{131}I) renogram and to demonstrate that by using this compound one can achieve a dependable renal clearance, and split renal function studies.

In previous publications we have shown a close correlation between simultaneous Renografin (^{131}I) renal clearance and inulin clearance in unanesthetized normal dogs (ratio 0.9) (1). In the present investigation we have applied this experience to 83 patients with a number of different urinary tract abnormalities.

Table I presents normal values for renal function in man according to Homer Smith. In our laboratory, the normal values for dogs have been compared with Homer Smith's normal dog values, and the ratio of these two applied to

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Homer Smith's man data have given us "normal man values" as shown. Using the clearance ratio of $\frac{\text{Renografin } (^{131}I)}{\text{Inulin}}$ we have derived our comparable normal values for "Renografin (^{131}I) clearance for man". This is justified by virtue of the extensive experience in our laboratory with PAH, inulin and Renografin (^{131}I) clearance determinations over several thousand experiments in unanesthetized dogs and a period covering approximately five years.

Our patient population in this study has included a total of 83 patients, 24 of whom had split-function determinations by the conventional methods of catheterization of one ureter with a second catheter in the urinary bladder. The remainder of these 83 patients had simultaneous renal clearance determinations but no catheterization of either kidney. Twenty of the total number presented sufficient data for analysis of Renografin (^{131}I) renograms in relation to urine flow rate. In every instance, however, simultaneous inulin, PAH and Renografin (^{131}I) clearance determinations were compared one with the other for each kidney where split-function determinations were obtained; or for the combined renal function where no ureteral catheters were *in situ*. The patients included

TABLE I

RENAL FUNCTION IN NORMAL MAN ACCORDING TO HOMER SMITH AND RELATED[1] VALUES FOR OUR LABORATORY (PER 1.73 M^2)

	Males, H. Smith	*Males, Our Lab.*	*Females H. Smith*	*Females Our Lab.*
Clearance, Inul. ml/min	124 ± 25.8	97.3 ± 20.2	109 ± 13.5	85.5 ± 10.6
Clearance PAH ml/min	654 ± 163	568 ± 142	592 ± 153	515 ± 133
Inulin/PAH Filtration Fraction × 100	19.2 ± 3.5	17.1 ± 3.1	19.4 ± 3.9	16.6 ± 3.4
[1]Renografin(^{131}I)	——	87 ± 18	——	77 ± 10

[1]Relationship obtained as follows:

$$\frac{\text{Our laboratory normal dog value}}{\text{Homer Smith normal dog value}} = F$$

Homer Smith "Man Value" × F = Our value for man

Our laboratory Clearance Ratio of $\frac{\text{Renografin}}{\text{Inulin}} = 0.9$

many different primary diagnoses such as pyelonephritis, glomerulonephritis, renovascular hypertension, essential hypertension, urinary tract calculi, carcinoma of the urinary bladder, hypoplastic kidney and various types of urinary tract obstructions.

In each instance, Renografin (^{131}I) renograms were obtained in the recumbent position with probes carefully placed under each kidney area at the same time the clearance determinations were done. In many instances, ortho-iodo-hippuric (^{131}I) acid renograms were also performed.

BASIC CLEARANCE PROCEDURES

Patients were all hydrated orally one-to-two hours prior to the procedure, with approximately 6 ml of water per pound, and maintained with 150 ml of water every half-hour thereafter throughout the entire test. An intravenous drip technique for hydration was preferred, at a rate of 40 to 60 drops per minute (2.5 to 3.5 ml/min) with five per cent glucose in water, and more recently, with 25% Mannitol in 400-500 ml five per cent glucose in water for diuresis. In addition, the sustaining solution contained 54 ml of inulin, 10% solution; 10 ml of PAH, 20% solution; and 0.5 ml of Renografin solution. Priming solutions were used as follows: 10% inulin, 50 milligrams per kilogram body weight; 0.5 ml Renografin; and 20% PAH (as sodium salt), eight milligrams per kilogram body weight. The priming and intravenous sustaining solutions were established at least 45 minutes prior to the clearance procedure.

Five minutes before the first clearance period was to begin, Renografin (^{131}I) was administered intravenously as a bolus, 10 μC per patient and a renogram recording obtained over each kidney. Simultaneous recordings over the heart and/or head, and over the urinary bladder were obtained wherever feasible.

In those patients who did not have a catheter in the urinary bladder, the patient emptied the urinary bladder voluntarily and this urine was discarded. In patients with a catheter in the urinary bladder, all urine was withdrawn and the collection bottle replaced. The collection periods were twenty minutes. Three 20 minute clearance periods were thus obtained.

An indwelling needle was inserted in a vein for withdrawal of blood samples. Three-to-five ml blood samples were drawn at two-to-five minute intervals and at least one 10 ml sample was obtained in the middle of each 20 minute clearance period. The blood was transferred to a heparinized tube and aliquots withdrawn for the following:

A. Hematocrit determination
B. Radioassay
C. Inulin assay
D. PAH assay

Thus, for each patient and/or each kidney, it was possible to make comparisons between PAH and inulin clearance rate determinations, and Renografin (^{131}I) clearance as determined by conventional radioisotopic assay; as well as calculated from the renograms over each kidney.

Qualitative assay of the hipputope and Renografin (^{131}I) renograms was

also carried out and the renograms denoted as either abnormal or normal. The renogram was considered as abnormal if it appeared so in any of its phases.

Filtration fractions of $\frac{\text{inulin}}{\text{PAH}}$ or $\frac{\text{Renografin } (^{131}\text{I})}{\text{PAH}}$ were also recorded.

METHOD USED IN SUBSTITUTING BLADDER PROBE TECHNIQUE FOR URINE COLLECTION IN "UV" DETERMINATION

In the conventional clearance studies by Homer Smith technique (4), clearance is calculated by the formula:

$$(1) \quad (C)\ \text{Clearance} = \frac{(U)\ \text{Urine concentration of test substances /cc} \times (V)\ \text{Volume of urine/min}}{(P)\ \text{Plasma concentration/cc of test substance in middle of test period}}$$

In order to eliminate the necessity for catheterization and urine collection for each clearance period, and in order to determine the quantity UV, a bladder probe technique may be substituted with reliable results. A scintillation detector

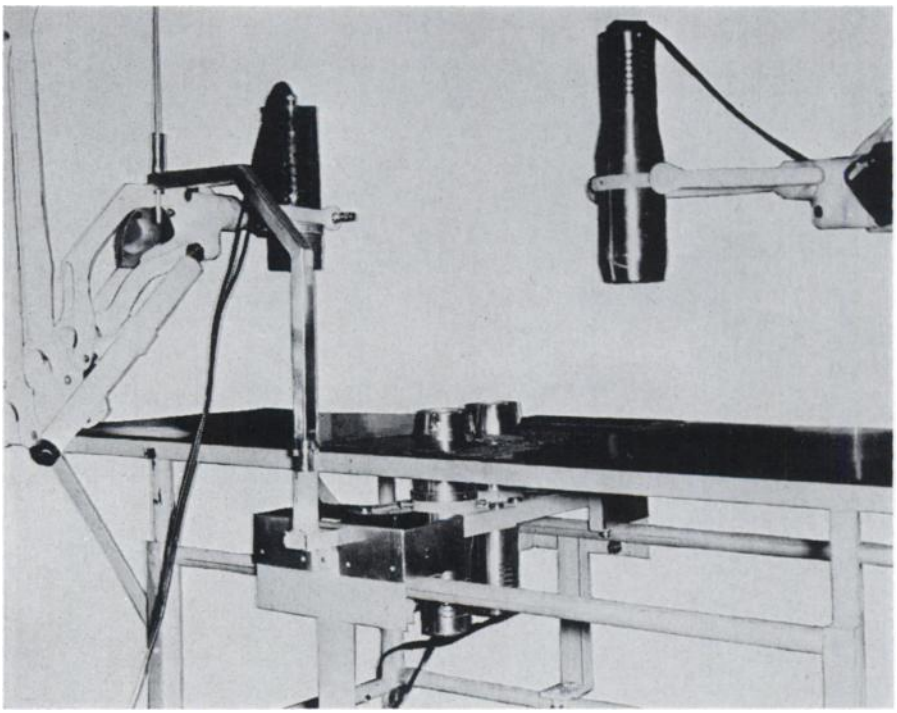

Fig. 1a. Special table designed for renograms. The patient lies supine. The kidney probes are adjusted over the kidney either by prior x-ray localization of kidneys or by minimal tracer dose administered just prior to renogram study. A third probe is placed over the urinary bladder and the fourth probe is placed over the temperoparietal region of the skull (by present techniques) or over the heart by former techniques. Each probe is balanced and calibrated. The recordings from each probe are connected to a tape recorder and ink writing rectilinear chart recorder. The constant infusion stand is also incorporated as part of the table (on left).

with flat field collimation similar to the kidney probes may be used for this purpose. While it is perhaps best to have a scaler for the read-out, if proper care is taken, a ratemeter alone will give good results.

Using a body and bladder phantom (Fig. 1), the bladder probe can be easily standardized. To determine the cpm/μC at a given distance, a standard source of approximately 10 μC ^{131}I is injected into the phantom bladder which contains approximately 400 cc water (a condom may be used as the bladder phantom).

The bladder phantom is then submerged into the body phantom which contains a 20 cm depth of water and an ^{131}I concentration five per cent that of the bladder phantom.

The probe is then placed in position over the bladder phantom at a probe-surface to center-of-phantom distance (PSPD) of 25 centimeters. The counts per minute (CPM) were obtained. A second count is made using a lead shield one inch thick and six inches in diameter placed over the bladder phantom. The count then obtained is subtracted from the first count, in order to correct for background, to obtain the net CPM. By dividing the net CPM by the number

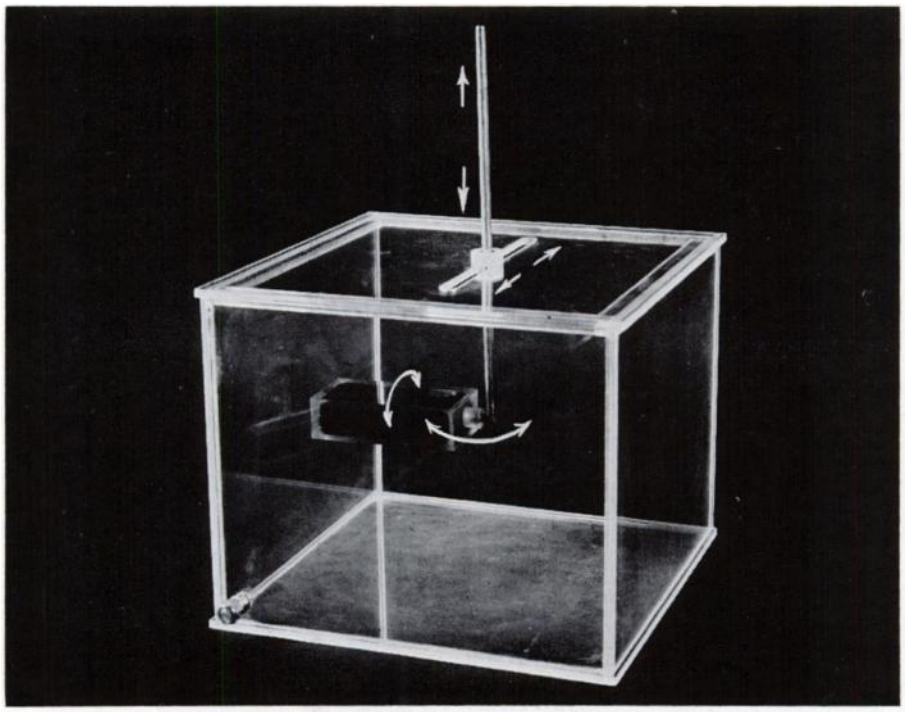

Fig. 1b. Phantom utilized for calibration of bladder probe and kidney probes. The mock kidney is shown in the photograph. A mock bladder can be similarly suspended an appropriate distance from the surface. An effort is made to have the mock bladder and/or kidney contain a quantity of nuclide which will simulate the content of the appropriate organ, and the surrounding liquid likewise contains a quantity of nuclide which will simulate the body environment.

of microcuries in the bladder phantom, the CPM per microcurie (μC) is obtained.

The calibrated probe is then placed over the patient's bladder at 25 cm PSPD. (The center of the patient's bladder may be assumed to lie 5 cm below the surface.) The net CPM may be obtained at the beginning of the period, as with the phantom, and again at the end of the period, and the background subtracted when the lead shield covers the urinary bladder. The difference obtained by subtracting the first net CPM from the second represents the total microcurie increment in the urinary bladder in the period. When this value is divided by the cpm per μC, UV is calculated for the clearance period.

Assuming a clearance period of 20 minutes duration, and a urinary excretion of 1.14 μC for the clearance period, a blood level of .00115 μC/cc, and hematocrit of 45%, the clearance is:

$$(2) \qquad \frac{\dfrac{1.14\ \mu C}{20\ \text{min}}}{\dfrac{.00116\ \mu C/cc}{1-\ .45}} = 27\ \text{cc/min}$$

METHODS OF HANDLING DATA

A description of Renografin (^{131}I) "Renovasculogram" is seen in Figure 2.. In contradistinction to the conventional renograms, where the chart recorder moves at a contant rate throughout the entire period of recording, we have adopted the concept that a much more rapid recording is necessary for the first 45 seconds-to-one minute giving us a more accurate depiction of the vascular phase. In order to differentiate this type of chart record from the conventional uniform speed record, we have applied the term "renovasculogram" to the type

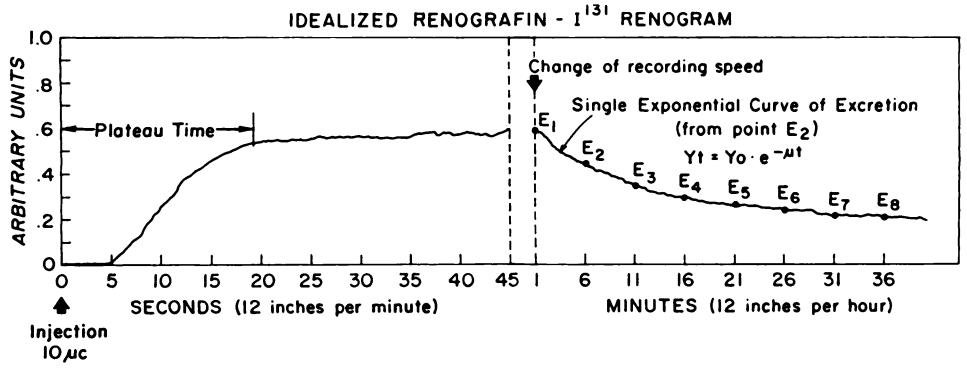

Fig. 2a. Idealized Renografin (^{131}I) renogram. The first part of the record is obtained at rapid speed—the second part at slow speed. The Y axis values are arbitrary values read off the chart (E1, E2, etc). These values are fed into a 1620 IBM computer and in most instances follow closely a single exponential equation. The regression coefficient is obtained by programming the computer accordingly. This value is utilized for calibration of clearance as indicated in the text. A reasonably accurate regression coefficient can be obtained by manually graphing the values on semilogarithmic paper, determining half-time of clearance and utilizing the values of the half-time for calculation of the regression coefficient (see formulae indicated in text).

of record where the first one minute of the record is obtained at 12 inches per minute in contrast to the last part of the record which is obtained at 12 inches per hour.

In previous descriptions from this laboratory (2,5), the renovasculogram for ortho-Iodo-hippuric (^{131}I) acid (Hipputope) has been analyzed. There is an initial latent phase until the radioistopic bolus reaches the renal artery at which time there is a rapid rise of the chart record to a relative plateau. This plateau then, continues with a very slow rate of rise for approximately two minutes. We have made it a practice to record this plateau for approximately 40 to 60 seconds. Thereafter the chart speed is changed to the slower pace and for the Hipputope renogram, the "secretory phase" is recorded. We have indicated the time to achieve a plateau as the plateau time. We have thereafter divided the renovasculogram into "secretory and excretory phases" and indicated each by measurable secretory and excretory half-times (7).

The Renografin (^{131}I) renovasculogram has been similarly recorded with the first 45 seconds to one minute being recorded at the rapid phase of 12 inches per minute, and then a change of chart speed to a record of 12 inches per hour. When the patient has been properly "equilibrated", the so-called "secretory" peak which is characteristic of the Hipputope renogram is ordinarily not present.

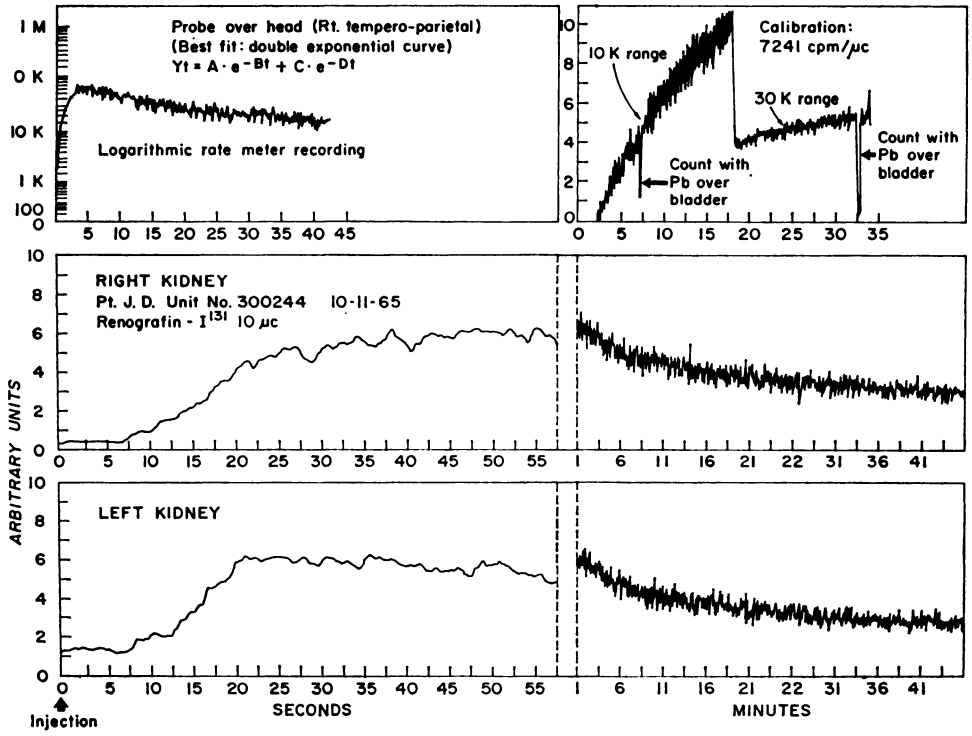

Fig. 2b. Representative curves obtained from the four probes. Upper left, recording from head and/or heart monitor (logarithmic ratemeter in this instance). Upper right, bladder probe recording. Lower two curves are the renogram curves, per se.

However, when the patient is not properly "equilibrated" one often does obtain a small peak. We have interpreted this peak as an indication that the interstitial body space has been instantaneously flooded with radioactive material. Since there has been no equilibration, a re-entry of the test agent from this interstitial space into the blood pool gives rise to this peak. *Characteristically, therefore, the Renografin (^{131}I) renogram, when proper equilibration and sustaining solution have been maintained, is merely characterized by an appearance period, a plateau, and slow excretory fall.*

By regression analysis with the Model 1620 IBM computer it has been determined that the curve usually produced by the Renografin (^{131}I) renovasculogram in approximately two-thirds of the cases, best fits a single exponential equation beyond the first five minute period. This single exponential equation may be expressed as follows:

(3) $Y_t = Y_o e^{-\mu t}$ where:

Y_t = activity over the kidney at any time, t

Y_o = activity over the kidney at time t_o

μ = the regression coefficient or the coefficient of clearance

t = the time elapsed after t_o

In a few instances the regression curve appears to fit a summation of two exponentials as follows:

(4) $Y_t = Ae^{-bt} + Ce^{-dt}$, where A and C are constants.

It is probable that when the single exponential equation is not the best fit for the excretory phase after the first five minutes, that an abnormal situation exists within either the arterial supply to the kidney, the kidney parenchyma or urine flow.

CHARACTERISTICS OF THE CURVE OBTAINED OVER THE HEART AND/OR HEAD

The disappearance curve obtained over the heart and/or head is usually characterized by a rise to a plateau which resembles closely the initial vascular or appearance phase of either type renogram (Fig. 2). After a short peaking and/or small plateau, there is a fall of the activity level. By regression studies with the Model 1620 IBM computer it has been determined that the excretory phase of this curve usually best fits a summation of two exponentials rather than the single exponential equation. When one obtains sequential blood samples and assays these for radioisotopic content, a similar curve is obtained corroborating this concept. In our description of results we have referred to the first exponential in the blood curve as the "B" coefficient; and the second exponential as the "D" coefficient. Various correlation studies have been made in relation to these two coefficients of the blood curve.

THE DISAPPEARANCE CURVE FROM THE PROBE OVER THE HEART (BLOOD CURVE)

All efforts to achieve a formula for clearance which might encompass a relationship of the blood disappearance curve to the Renografin (^{131}I) renogram

disappearance curve have thus far not been successful.

The correlation coefficient of the clearance coefficients (μ) of the Renografin (^{131}I) renogram, when this is expressed as a single exponential with the B and D coefficients of the heart probe, are .385 and .395 respectively in 19 cases, giving a level of significance p value of less than 0.1. All other correlations attempted were poor.

Thus, although it would appear that the disappearance curve over the heart might have a meaningful relationship to the disappearance of the Renografin from the kidney, we have not thus far been able to equate this relationship.

METHOD OF CALCULATING CLEARANCE FROM THE RENOGRAFIN (^{131}I) RENOGRAM

The method which thus far has yielded the most satisfactory prediction of Renografin (^{131}I) clearance from the Renografin renogram curve is as follows:

(5) $Y_t = Y_o\, e^{-\mu t}$ as indicated previously. On such an equation the half-time relationship $t_{\frac{1}{2}}$ of the curve is as follows:

(6) $t_{\frac{1}{2}} = \dfrac{-\ln 1/2}{\mu}$ where

$-\ln_{\frac{1}{2}}$ = the natural logarithm of 1/2, 0.693

The value of μ in this equation is:

(7) $\mu = \dfrac{\log Y_t/Y_o}{t}$

We have utilized the Model 1620 IBM computer for calculation of μ from the values obtained from the renogram itself.

The half-time values may thereafter be calculated by substituting in equation (2).

The clearance values for each patient were then related to the corresponding half-time values as calculated in the following manner:

(8) $C\alpha \dfrac{1}{t\ 1/2}$

From this relationship it also follows that:

(9) $C\alpha \dfrac{1}{\dfrac{-\ln 1/2}{\mu}}$, substituting the denominator value for t 1/2 as derived in equation (2).

(10) $C\alpha \dfrac{\mu}{-\ln 1/2}$ or $\dfrac{\mu}{0.693}$

In order to arrive at a proportionality constant, for this equation, the inulin clearance values for 20 cases were related directly to 1000 x the reciprocal of the clearance half-time as calculated above. The clearance values were, in each case, approximately twice the reciprocal of the half-time x 1000. (The value,

1000, can be justified on the basis of the arbitrary strip chart paper units which are expressed in values from .0 to 1.0 and from which the data for the half-time were determined.) It was decided to test "e", the base of natural logarithms as follows:

$$(11)\ C = K\frac{\mu}{-\ln 1/2}$$

$$(12)\ K = 1000\, e^{-\ln 1/2}$$

$$(13)\ C = \frac{1000\, e^{\ln 1/2}\,\mu}{-\ln 1/2} = \frac{2000\,\mu}{.693}$$

$$(14)\ C = 2886\,\mu$$

This empirically determined equation was then tested in individual cases and the following data obtained:

In those 20 cases where combined clearance of both kidneys was determined and Renografin (^{131}I) renograms were available, as well as urine flow determinations, it was found that there was excellent agreement of calculated total clearances from the renograms in 12 of the cases (correlation coefficient 0.92), where the urine flow was 2 ml per minute or greater. In the eight cases where urine flow was less than 2 ml per minute, calculated clearances were very poor [correlation coefficient (−)0.41].

This would indicate that, for accuracy, urine flow greater than 2 ml per minute must be maintained. It is our present technique to incorporate 100 ml to 200 ml Mannitol (25% solution) per 500 ml of isotonic dextrose infusate for this purpose.

DETERMINATION OF RENAL SPLIT-FUNCTION BY USE OF SIMULTANEOUS RENOGRAFIN (^{131}I) RENOGRAMS

In some patients, where a ureteral catheter is not present, split-function may be calculated if one knows the combined clearance from both kidneys.

Clearance (C) is determined in a conventional fashion by collecting the urine or by placing a probe over the urinary bladder, by determining the concentration of the test agent in the urine (U), the volume of urinary excretion in the test period (V), and the concentration of the test agent in the plasma in the middle of the test period (P). This is the classical technique developed by Homer Smith ($C = \frac{UV}{P}$).

Since the single exponential equation clearance is directly proportional to the regression coefficient (μ), we can derive the further proportionality. The clearance of the right kidney when compared to that of the left kidney, is proportional to the regression coefficient of the right kidney (μ_R) when compared to the regression coefficient of the left kidney (μ_L). Knowing the combined clearance by actual determination, it is very simple thereafter to determine the split-renal function:

$$(15)\ \text{Total Clearance} = C_R + C_L$$

$$(16)\quad \frac{\text{Clearance Rt. Kidney } (C_R)}{\text{Clearance Lt. Kidney } (C_L)} = \frac{\mu \text{ rt. kidney}}{\mu \text{ lt. kidney}}$$

This may be used as an additional check on the accuracy of the clearance calculation from each kidney, from the renogram curves (equation 14), since the two calculated clearances should equal the radioassayed combined clearance value.

It is important when clearance is calculated in this manner, that the volume of urine (or the quantity of nuclides) accumulated within the bladder within the test period be known accurately. Best results are obtained with either the probe technique over the urinary bladder, or utilizing a catheter in the bladder, with irrigation of the bladder using 20 ml of isotonic saline.

Unfortunately, in many patients, voluntary voiding does not empty the bladder completely, and the "UV" part of the clearance formula would then be inaccurate.

It is also desirable during the clearance period to obtain several sequential blood samples rather than placing reliance on a single sample. Thereby, the average "P" value in the clearance formula becomes more accurate.

SUMMARY

1. Although the Hipputope renovasculogram is perhaps easier to evaluate qualitatively by the uninitiated, with a moderate degree of experience, a similar order of accuracy can be achieved for the evaluation of a Renografin (^{131}I) renogram.

2. The excretory phase of the Renografin (^{131}I) renogram beyond the first five minutes can usually be expressed by a simple single exponential equation.

3. By utilizing this single exponential equation and the charted values in the excretory phase of the Renografin (^{131}I) renogram, we have described a method whereby the Renografin (^{131}I) clearance can be calculated with an acceptable accuracy in a significant number of cases, provided urine flow is maintained above 2 ml per minute. With the equation $C = 2886\ \mu$, where μ is the regression coefficient obtained from this single exponential equation, the Renografin (^{131}I) clearance may be calculated with a p value of better than 0.01.

4. It has been demonstrated that both in the normal as well as in the abnormal state, Renografin (^{131}I) clearance closely follows inulin clearance, and hence may be assumed to represent a good test for glomerular filtration (1,3).

5. It is our present opinion that our radioisotopic evaluation of renal function can readily include the following: (a) A Hipputope renogram particularly valuable for qualitative assay. (b) A Renografin (^{131}I) renogram valuable not only for its qualitative assay of renal function, but also for a quantitative description of glomerular filtration. (c) A Renografin split-function, quantitated from the renogram, and from the combined Renografin (^{131}I) clearance.

6. The Renografin (^{131}I) clearance for each kidney is a test of glomerular filtration. It remains to be seen whether this split-function test is of value in the clinical evaluation of renovascular hypertension, and other clinical states.

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REFERENCES

1. MESCHAN, I., DEYTON, W. E., SCHMID, H. E. AND WATTS, F. C.: The utilization of ^{131}I labeled Renografin as an inulin substitute for renal clearance rate determination. *Radiology*, 81:974-979, 1963.

2. MESCHAN, I., SCHMID, H. E., WATTS, F. C. AND WITCOFSKI, R. L.: The utilization of radioactive iodinated Hippuran for determination of renal clearance rates. *Radiology* 81:437-446, 1963.

3. MORRIS, A. M., ELWOOD, C., SIGMAN, E. M., CATANZARO, A.: The renal clearance of I^{131} labeled meglumine diatrizoate (Renografin) in man. *J. Nucl. Med.* 6:183-191, 1965.

4. SMITH, H. W.: Principles of Renal Physiology. *Oxford University Press*, New York, p. 32, 1956.

5. WHITLEY, J. E., WITCOFSKI, R. L. AND MESCHAN, I.: Experimental comparison of ortho-iodo-hippuric acid and iodopyracet in renal function evaluation. *Radiology* 76:464-466, 1961.

6. WINTER, C. C.: Editorial. Quantitative versus qualitative interpretation of the radioisotope renogram. *J.A.M.A.* 192:1089, 1965.

7. WITCOFSKI, R. L., WHITLEY, J. E., MESCHAN, I., AND PAINTER, W. E.: A method and parameters for the analysis of renal function by external scintillation detector technique. *Radiology* 76:621-628, 1961.