THE INFLUENCE OF TISSUE BACKGROUND RADIOACTIVITY ON THE APPARENT RENAL ACCUMULATION OF RADIOACTIVE COMPOUNDS

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Following intravenous injection of radioactive compounds that are selectively accumulated in the kidney, measurements over the renal area show variable periods of increasing radioactivity. The rising portion of such curves has been used as a measure of individual kidney function or blood flow (*1–3*). The compound most frequently employed in such studies is ^{131}I-Hippuran, which usually shows continuing accumulation in the renal areas for 2–5 min (*2*). Mercury-203-chlormerodrin, which is bound to renal tubular epithelium, continues to show accumulation for about 60 min.

Proposed methods of evaluating differences of blood flow or function between the kidneys are based on differences in the shapes of the curves of renal-area accumulation. Reba *et al* (*3*) demonstrate changing ratios of radioactivity between the kidneys in patients with unilateral renal disease following ^{203}Hg-chlormerodrin injection. Their data indicate that the better or uninvolved kidney accumulates a progressively greater percentage of the radionuclide than the diseased kidney during the course of 1 hr. Taplin *et al* (*2*) apply essentially similar reasoning to the accumulation phase of ^{131}I-Hippuran curves but express the differences between the kidneys in terms of slopes of the rising curves.

In these studies the detectors view not only the kidneys but a considerable volume of other tissues, and the curves of radioactivity in these areas differ considerably from those of the kidney itself (*4*). The present studies were designed to evaluate the magnitude of tissue background radioactivity in the renal-area curves and to assess the effect of tissue background on apparent differences between the kidneys in the rate of renal accumulation of labeled compounds in certain renal disorders.

MATERIALS AND METHODS

The ^{131}I-Hippuran studies were performed in four patients with proven unilateral renal arterial disease, in three normal subjects and in one patient with unilateral chronic pyelonephritis. The ^{203}Hg-chlormerodrin studies were performed in two of the above patients with arterial disease, in the patient with chronic pyelonephritis, in two additional normal subjects and in three additional patients with proven unilateral renal arterial stenosis. All normal subjects were studied with one renal-area probe deliberately positioned caudal to the renal area to produce a partial view of the kidney, a correspondingly lower counting rate and different percentage contribution of tissue background.

The detectors and recording system have been previously described (*4*). The patients were seated. Following bolus injection of the radioisotope (30–50 μCi), continuous simultaneous recording of the pulses from detectors placed over each renal area, the bladder and upper chest was made on four-track magnetic tape. Data from the magnetic tape were displayed as the usual analog curves and integrated to yield counts accumulated per selected time interval. The Hippuran studies were integrated at 4.0-sec intervals until the time one curve began to fall; the chlormerodrin studies were integrated at 40-sec intervals up to 1 hr.

It was previously suggested that the upper chest radioactivity curves mimic those from a nephrectomized area and can be used as a measure of tissue background (*4*). To extend these observations, the counting rate of the upper chest was compared to a nephrectomized area following the injection of ^{131}I-Hippuran in 11 patients and in 10 studies in seven dogs. Since close correspondence of the values was obtained (see Results) the chest curve was treated as background in subsequent patient studies. The integrated counts for each interval of the chest data were subtracted from the corresponding interval of each renal area to yield net kidney counts.

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The ratios of total radioactivities in the renal areas and the ratios of net kidney counts at successive times as well as the percentage contribution of tissue background to each renal area at various times were calculated. The ratios were obtained by dividing the lesser counting rate by the greater. The total kidney-area counts and net kidney counts were plotted semilogarithmically. Semilogarithmic plots of curves with proportionally similar changes but differing only in magnitude are parallel. Curves differing in their rate of change will diverge or converge.

A mathematical construct was made to demonstrate the effect of the same tissue background on the shape of renal-accumulation curves, where the net kidney curves differ in counting rate only by a constant factor. The net counts per 40 sec from a single kidney of a normal subject studied with ^{203}Hg-chlormerodrin were multiplied by 1.5 to give two net kidney curves that differed only by this factor. The same chest background was then added to each to simulate total renal-area curves, and the curves were then analyzed as above.

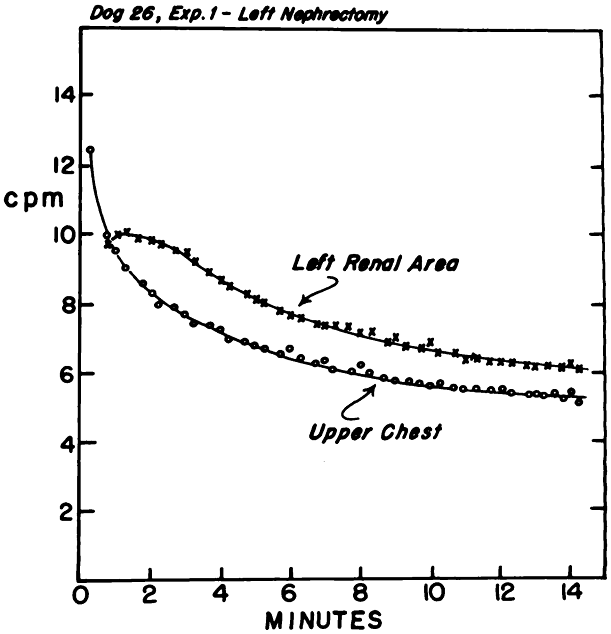

FIG. 1. Comparison of upper chest and nephrectomized renal area curves in dog.

RESULTS

Comparison of upper chest and nephrectomized area counting rates. The validity of using the upper chest as a background for the renal area was established in 10 experiments in seven dogs and in 11 patients. After unilateral or bilateral nephrectomy was performed in dogs, ^{131}I-Hippuran was given and the counts of the renal area were compared with those of the upper chest at selected intervals. Figure 1 illustrates the results in one dog. Table 1 presents the ratios of the counting rates in the chest and renal areas, the means and standard deviation of the group at each selected time interval and the standard deviation of the ratios over the entire period of observation in each experiment.

In the individual studies within the selected time of observation, the standard deviations of the ratios range from 0 to 8% with an average of 3.7%. Among the group the standard deviations of the ratios at each point in time range from 18% (mean 1.06) at 1 min to 11% (mean 1.07) at 12 min. At 1–2 min after injection a renal area with an intact kidney has 4–5 times the counting rate of the chest area. Therefore, use of the chest as a measure of renal area tissue background will introduce a maximum of 10% error (±2 s.d.) in the net kidney curve. By the twelfth minute the counting rate of the chest is about 40% of the renal area with an intact kidney. The smaller variation of the chest-to-

TABLE 1. RATIOS OF UPPER CHEST AND NEPHRECTOMIZED RENAL AREA RADIOACTIVITIES (CHEST/RENAL AREA) IN DOG

		Ratios at:							
Dog #	Exp.	1 min	2 min	4 min	6 min	8 min	12 min	Mean	s.d.
9	4	0.82	0.85	0.88	0.90	0.92	0.96	0.89	0.05
13	3	1.28	1.28	1.26	1.25	1.24	1.21	1.25	0.03
17	1	0.72	0.81	0.85	0.89	0.92	0.97	0.86	0.04
	2	0.93	1.0	1.0	1.0	1.0	1.0	0.99	0.02
18	3	1.20	1.21	1.21	1.21	1.21	1.20	1.21	0.01
21	3	1.11	1.22	1.11	1.05	1.02	0.98	1.08	0.08
29	1	1.23	1.15	1.10	1.08	1.07	1.05	1.11	0.06
	2	1.14	1.11	1.09	1.08	1.07	1.06	1.09	0.02
	3	1.04	1.04	1.04	1.04	1.04	1.04	1.04	0.
26	1	1.08	1.18	1.22	1.23	1.24	1.26	1.20	0.06
Mean		1.06	1.08	1.08	1.07	1.07	1.07		
s.d.		0.18	0.16	0.14	0.13	0.12	0.11		

TABLE 2. RATIOS OF UPPER CHEST AND NEPHRECTOMIZED RENAL AREA RADIOACTIVITIES (CHEST/RENAL AREA) IN PATIENTS

		Ratio at:								
Patient #	Diagnosis	1 min	2 min	4 min	8 min	12 min	16 min	20 min	Mean	s.d.
554	R. Nephrectomy	1.00	1.00	1.04		1.02	1.02	1.04	1.02	0.027
597	R. Nephrectomy	1.00	0.94	0.89	0.79	0.81	0.83	0.79	0.86	0.082
610	L. Nephrectomy	1.29	1.30	1.24	1.16	1.14	1.16	1.13	1.20	0.069
617	L. Non-funct.	0.75	0.76	0.77	0.76	0.75	0.76	0.75	0.76	0.071
636	L. Nephrectomy	1.18	1.25	1.22	1.12	1.15	1.15	1.16	1.18	0.045
639	L. Non-funct.	1.00	1.00	0.94	0.89	0.92	0.91	0.94	0.94	0.058
642	L. Non-funct.	1.14	1.07	1.00	1.00	1.00	1.00	1.00	1.03	0.078
653	L. Cong. absence	1.28	1.21	1.14	1.10	1.08	1.10	1.12	1.15	0.095
655	L. Nephrectomy	0.98	0.98	0.96	0.94	0.92	0.90	0.91	0.94	0.033
656	R. Nephrectomy	0.90	0.89	0.89	0.88	0.85	0.83	0.83	0.87	0.030
667	L. Non-funct.	0.80	0.82	0.78	0.78	0.75	0.75	0.73	0.78	0.032
Mean		1.03	1.02	0.99	0.94	0.94	0.95	0.95		
s.d.		0.18	0.17	0.14	0.15	0.15	0.15	0.16		

TABLE 3. RATIOS OF RENAL RADIOACTIVITIES—^{131}I-HIPPURAN

			Time (sec)											% Tissue background	
Patient	Ratio		20	40	60	80	100	120	140	160	180	200		40 sec	Peak
1*†	L/R	Total	0.81	0.78	0.77	0.76							L	48	45
		Net	0.65	0.66	0.66	0.66							R	38	36
2†	R/L	Total	0.72	0.67	0.65	0.64	0.62	0.60					R	67	51
		Net		0.43	0.44	0.44	0.44	0.45					L	49	31
4*†	R/L	Total		0.71	0.64	0.62	0.62	0.60	0.59	0.59	0.59		R	81	63
		Net		0.35	0.35	0.34	0.34	0.35	0.34	0.34	0.34		L	62	36
5†	L/R	Total	1.00	1.00	1.00	1.00	1.00	1.00					L	15	13
		Net	1.00	1.00	1.00	1.00	1.00	1.00					R	15	13
6*‖	L/R	Total	0.86	0.85	0.84	0.83	0.85	0.82	0.82	0.82			L	42	27
		Net	0.76	0.75	0.77	0.77	0.77	0.78	0.78	0.78			R	34	24
7‡	L/R	Total	0.88	0.83	0.80	0.79	0.78	0.78	0.77	0.77			L	45	26
		Net	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.71			R	35	20
8‡	R/L	Total	0.73	0.73	0.71	0.71	0.69	0.68	0.65	0.63	0.61		R	71	41
		Net	0.47	0.46	0.47	0.47	0.47	0.47	0.47	0.47	0.47		L	55	26
9‡	R/L	Total	0.79	0.77	0.76	0.76	0.75	0.74	0.72	0.71	0.70	0.68	R	44	23
		Net	0.64	0.63	0.64	0.65	0.65	0.66	0.65	0.65	0.65	0.65	L	32	19

* studied with ^{131}I-Hippuran and ^{203}Hg-chlormerodrin
† unilateral renal arterial stenosis
‡ mispositioned detector
‖ unilateral pyelonephritis

renal area ratios at this time maintains the maximum error in the net kidney curves at about 10%. Due to the constancy of the chest-to-kidney area ratio over an interval in each study, the introduced error will alter the shape of the net kidney curve only slightly.

Table 2 presents the ratio of counting rates of the upper chest and a nephrectomized renal area in eleven patients. The means and variability of the data are almost identical to similar observations in the dogs.

Comparison of renal accumulation of ^{131}I-Hippuran by the two kidneys in man. The accumulation of ^{131}I-Hippuran by the kidneys was studied in four patients with unilateral renal arterial stenosis proven by angiography, divided function studies and a hemodynamically significant lesion at surgery; in one patient with unilaterally predominant pyelonephritis by radiographic and urine culture criteria; and in three subjects in whom a difference in counting rate between the two kidneys was produced by deliberately positioning one renal probe caudal to the kidney.

Table 3 shows the ratio of counting rates of the two kidneys from time of appearance until the first loss of radioactivity to the bladder. The ratios of the total counts in the two renal areas and of the net counts obtained after subtracting tissue background (upper chest probe) and the percent background contribution to the renal area curves at selected times are presented. Patient #5, who had a cure of his hypertension following surgery, had superimposable curves of accumulation but vastly different curves in the descending portion. In the remainder of the studies the ratio of total radioactivity of the kidney with the lower initial counting rate (0–20-sec values) to its partner became progressively smaller as accumulation continued. The ratios of net counting rates of the two kidneys remain constant. Figure 2 is the semilogarithmic plot of the total and net counting rates of the two kidneys from one patient with renal arterial stenosis and demonstrates a divergence of the curves of total counts, and parallelism of the net curves.

Comparison of renal accumulation of ^{203}Hg-chlormerodrin by the two kidneys in man. Relative renal accumulation of ^{203}Hg-chlormerodrin by the two kidneys was studied for up to 60 min in five patients with unilateral renal arterial stenosis (two of the patients were also studied with ^{131}I-Hippuran), in the above-mentioned patient with pyelonephritis and in two additional subjects with one detector mispositioned. The criteria for the diagnosis of renal artery stenosis were as above. Table 4 presents the ratios of the two kidneys of both total and net renal counts and the percent background. Again, with time, the ratio of the total counting rate of the kidney with lesser uptake compared to its partner declines in each study except in Patient #12. This patient had superimposable left and right curves of accumulation despite hemodynamically significant unilateral renal arterial stenosis. The net curves show constancy of the ratio of the two kidneys during 45–60 min in all studies. Figure 3 is the semilogarithmic plot of the

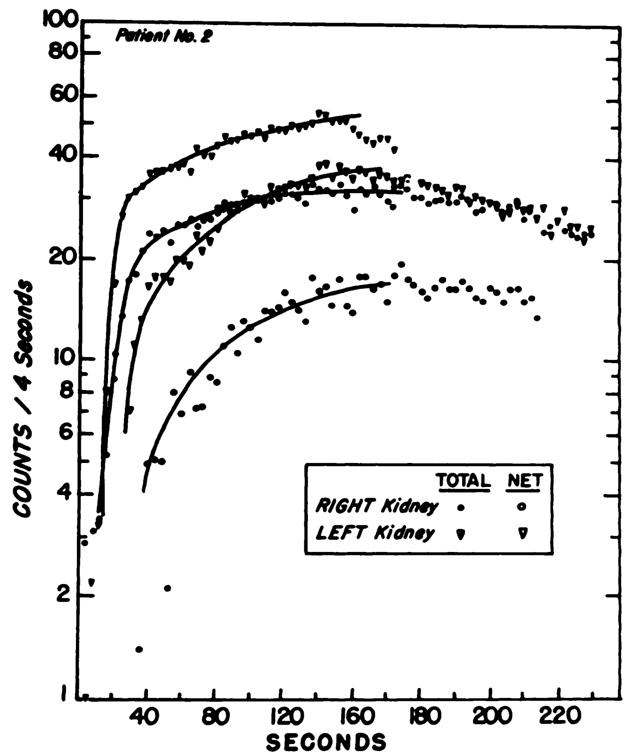

FIG. 2. Total and net counting-rate curves of renal accumulation of ^{131}I-Hippuran in patient with renal arterial stenosis. Total counting-rate curves diverge more than net counting-rate curves which are nearly parallel.

TABLE 4 RATIOS OF RENAL RADIOACTIVITIES—^{203}Hg-CHLORMERODRIN

Patient	Ratio		Time (min) 5	10	20	30	40	50	60		% Tissue background 5 min	Peak
1*†	R/L	Total	0.88	0.75	0.73	0.69	0.67	0.66		R	68	36
		Net	0.51	0.51	0.51	0.50	0.50	0.51		L	45	16
4*†	R/L	Total	0.74	0.68	0.65	0.63	0.58	0.53	0.50	R	70	24
		Net	0.46	0.46	0.51	0.51	0.48	0.46		L	49	12
10†	L/R	Total	0.81	0.75	0.70	0.67	0.65	0.64	0.63	L	76	37
		Net	0.50	0.52	0.51	0.51	0.51	0.51	0.51	R	60	23
11†	R/L	Total	0.94	0.92	0.88	0.85	0.84	0.83	0.82	R	69	22
		Net	0.77	0.79	0.79	0.78	0.77	0.77	0.77	L	53	19
12†	R/L	Total	1.00	1.00	1.00	1.00	1.00	1.00	1.00	R	35	11
		Net	1.00	1.00	1.00	1.00	1.00	1.00	1.00	L	35	11
6*‡	L/R	Total	0.86	0.84	0.83	0.81	0.78			L	47	24
		Net	0.73	0.75	0.76	0.77	0.75			R	38	20
3‖	R/L	Total	0.96	0.94	0.91	0.90	0.88	0.87	0.86	R	65	34
		Net	0.84	0.84	0.83	0.83	0.82	0.82	0.82	L	61	31
13‖	R/L	Total	0.69	0.68	0.67	0.66	0.61			R	60	28
		Net	0.51	0.54	0.54	0.54	0.55			L	48	19

* studied with ^{203}Hg-chlormerodrin and ^{131}I-Hippuran
† unilateral renal arterial stenosis
‡ unilateral pyelonephritis
‖ mispositioned detector

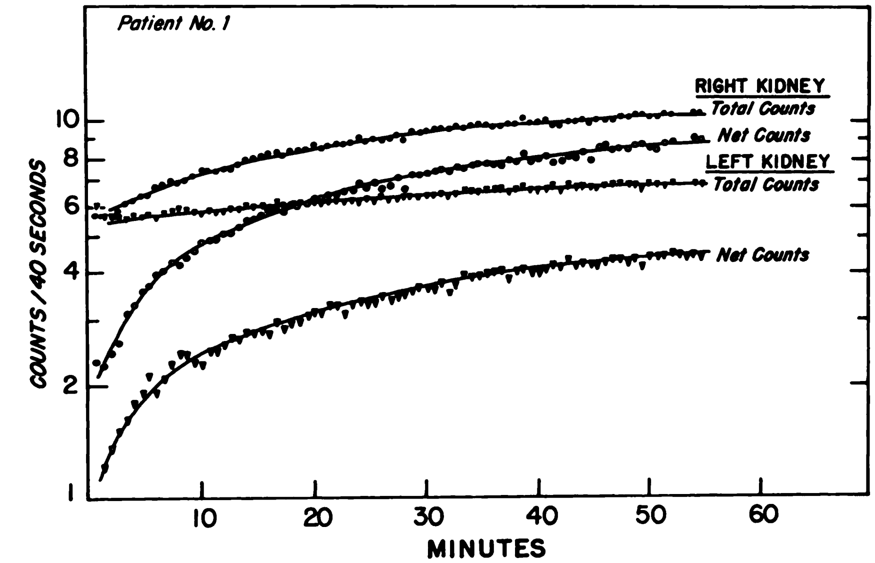

FIG. 3. Total and net counting-rate curves of ^{203}Hg-chlormerodrin accumulation in patient with renal arterial stenosis. Total counting-rate curves diverge (changing ratio) while net counting-rate curves are parallel (constant ratio).

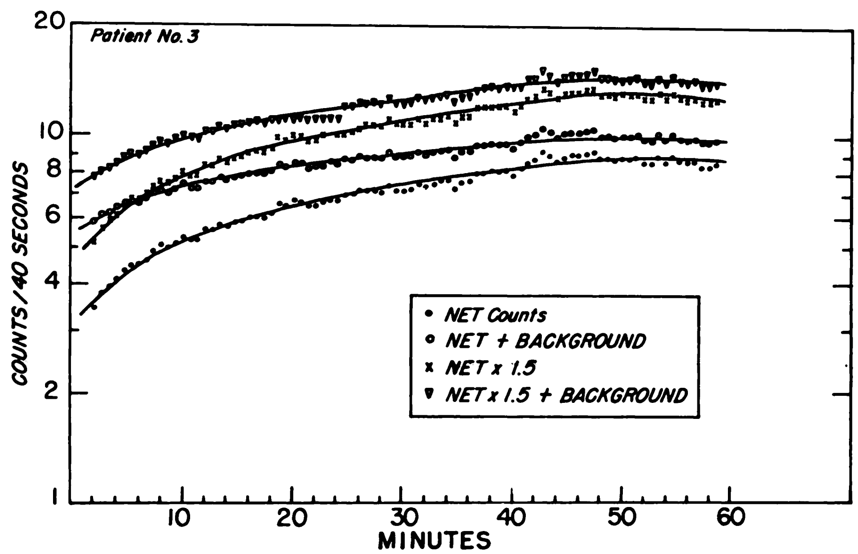

FIG. 4. Mathematical construct. Net renal accumulation curve of ^{203}Hg-chlormerodrin has been multiplied by 1.5. These two curves are parallel (constant ratio). Adding identical tissue background to each produces curves that diverge (changing ratio).

total and net counting rates of the two kidneys from one patient with renal arterial stenosis. The total counting-rate curves clearly diverge, while the net curves are parallel.

A mathematical construct. The effect of background was simulated in one study as described in Methods. Adding the background (upper chest) curve to a net kidney curve of a ^{203}Hg-chlormerodrin study and its 1.5 multiplicand produces curves which diverge as do the total counting-rate curves in the preceding studies (Fig. 4). The net curve and its 1.5 multiplicand are necessarily parallel in the semilogarithmic plot.

DISCUSSION

Relative blood flow and functional capacity of an individual's two kidneys may be assumed to be relatively constant for short intervals of time. With a constant ratio of blood flow and function of the two kidneys a constant ratio of accumulation from the blood would be anticipated. However, Reba, McAfee and Wagner (*3*) have reported the ratio of uptake of ^{203}Hg-chlormerodrin by the two kidneys to vary progressively in time in patients with unilateral renal disease of various etiologies. Taplin, Dore and Johnson (*2*) use the uptake phase of ^{131}I-Hippuran studies to detect unilateral reduction of renal blood flow in a manner that implies a changing ratio of radioactivity between the kidneys. The studies presented here confirm both of these observations if total counts in the renal area are used and if an initial difference in counting rate exists between the kidneys. However, subtraction of extrarenal tissue background radioactivity from the total curves gives net curves which have constant ratios during uptake as anticipated. Were sufficiently great differences in counting rate between the two kidneys present in all or most patients with unilateral renal disease, the indices described by Taplin and associates and Reba and coworkers would be empirically useful. In our experience, however, many patients with remediable hypertension due to unilateral arterial stenosis show little or no difference between the kidneys in uptake (Patients #5 with ^{131}I-Hippuran and #12 with ^{203}Hg-chlormerodrin in this small series). In a series of 58 patients with surgically proved renal arterial stenosis studied with ^{131}I-Hippuran, 28% showed equal uptake or even greater uptake by the diseased kidney (*5*). Another series of patients with unilateral renal artery disease studied with ^{131}I-Hippuran by Burbank, Hunt, Tauxe and Maher (*6*) also had patients with insignificant differences between the kidneys in the uptake phase.

Not only does the sensitivity of analyses utilizing the accumulation phase depend on fairly large differences in blood flow but the reverse phenomenon may also occur. Significant differences in counting rate between the kidneys due to geometrical, sensitivity or positioning factors may produce apparent differences of the accumulation rates although the kidneys do not functionally differ. The studies with the deliberately mispositioned probe and the mathematical construct show varying ratios of total counting rate between the kidneys similar to those seen in patients with unilateral renal disease.

A large discrepancy in renal size and function is present in most patients with renal arterial stenosis, and therefore most radiographic, radioisotopic or other functional tests detect a difference between the kidneys. A more difficult problem is presented in detecting those patients with small but significant differences between the kidneys. A method that is dependent on detecting differences in uptake would appear to be too insensitive in this critical situation. Differences of retention of radio-Hippuran by the two kidneys are an almost constant finding in renal arterial stenosis (*5*), and evaluations of the descending portion of the radio-Hippuran curves have proved to be quite sensitive in detecting this and other renal disorders (*5–7*). This type of analysis should be preferred, at least in patients with suspected renal artery disease.

SUMMARY

The use of the upper chest as a measure of nonrenal tissue background in the renal areas was validated in dogs and patients. The role of tissue background in altering the curves of renal accumulation of radioisotopes was then explored.

The ratio of renal accumulation by the two kidneys would, from physiological considerations, be expected to remain constant for short times. Comparison of total counts in the renal areas reveal a varying ratio of uptake in people with significant discrepancies in initial counting rate. After tissue background is subtracted, the net kidney curves show a constant ratio of uptake in time in all cases. Evaluations of renal functions based on comparisons of uptake are dependent on significant differences in initial uptakes. It is suggested that methods of evaluation that reflect renal retention of radioisotope are more sensitive in detecting renal artery disease.

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