OBSERVATIONS ON THE MECHANISM OF THE RENAL CLEARANCE OF I^{131} [1]

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Studies of the renal excretion of iodide have been reported from several laboratories in recent years (1–6).[3] Despite this accumulation of information, many properties of the renal mechanisms for excretion of the iodide ion remain unknown. The present study represents an attempt to explore the behavior of the renal clearance of I^{131} under a variety of experimental conditions in human subjects. The clearance of I^{131} has been determined simultaneously with other measurements of renal function and all values, including those for I^{131} clearance, were obtained using a continuous infusion technique. It is assumed that the data derived from the study of I^{131} may be applied freely to explain the behavior of stable inorganic iodide.

METHODS

Case material

The observations are based upon 58 renal clearance studies performed on 49 adult human subjects. Four general groups of patients were included:

1. *Euthyroid subjects with normal renal function:* Thirty-four clearance studies were performed on 31 subjects, all of whom were either convalescent hospitalized patients, or out-patients, without clinical or physiologic evidence of renal disease. The mean age was 33, with a range of 20 to 65 years.

2. *Euthyroid subjects with renal disease:* Thirteen studies were performed on seven patients. Four patients had polycystic renal disease, two chronic glomerulonephritis, and one probable chronic pyelonephritis. Glomerular filtration rates ranged from 9 to 100 cc. per min. per 1.73 sq. m. The mean age was 40 with a range of 23 to 75 years.

3. *Hyperthyroid patients:* The four subjects included in this group ranged in age from 21 years to 46 years and were clinically hyperthyroid at the time of study.

4. *Myxedema patients:* Five patients with primary myxedema and two patients with secondary myxedema were included in this group. The mean age was 40 with a range of 25 to 60 years.

Procedure

Simultaneous determinations of the clearances of inulin, PAH, and I^{131} were performed in all cases. In addition, the excretion rates and plasma levels of sodium, potassium, and chloride were determined during each clearance period. Standard continuous infusion techniques were employed for the measurement of the clearance of inulin and PAH and the continuous infusion method adapted, as previously reported (6), for the determination of the clearance of I^{131}.

All patients were fasting and recumbent at the time of study. In the typical experiment a liter of water was ingested 60 to 90 minutes prior to administration of the priming solution. Subsequent water intake varied with the nature of the experiment. Urine was collected through an inlying multiholed rubber catheter, and urine collections were concluded with two washouts of distilled water, followed by two or more injections of air. Following a timed blank urine collection period, a priming injection of inulin, PAH and I^{131} was administered intravenously and a sustaining infusion of the same substances (in a normal saline vehicle) was delivered by a Bowman constant infusion pump, usually at a rate of 1.5 cc. per min. A 30 to 40-minute period was allowed for equilibration of plasma concentrations, and in the typical experiment, at least three control clearance periods averaging 15 minutes in duration were obtained. When experimental conditions were altered after the control periods, three to seven additional periods were obtained.

Venous blood was sampled at the mid-point of each period through an inlying 17-gauge thin-walled needle, using approximately 0.1 cc. heparin for every 10 cc. of blood. The samples were centrifuged and separated without delay. Inulin was determined according to a modification [4] of the method of Roe, Epstein, and Gold-

[1] Presented in part at the 26th Annual Meeting of the Central Society for Clinical Research, Chicago, Illinois, October 30, 1953.

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[3] A discussion of the majority of these data is contained in a comprehensive review by Riggs (7).

[4] Modifications include: 1) Heating diluted plasmas and protein precipitating reagents in a 50-degree water bath for 30 minutes after shaking; 2) separation of protein-free filtrates by centrifugation rather than filtra-

stein (8); PAH, according to the method of Smith, Finkelstein, Aliminosa, Crawford, and Graber (9); chloride, according to the method of Van Slyke and Hiller (10); thiocyanate, according to the method of Gregersen and Stewart (11); and sodium and potassium were analyzed on an internally compensated Baird flame photometer. The details of the analytic methods employed in this laboratory for assay of I^{131} in plasma and urine have been reported in a separate communication (6). Donnan corrections were as follows: Na, 0.95; Cl, 1.02; and K, 0.95. I^{131} values were uncorrected.

RESULTS

I. *I^{131} plasma levels*

Continuous infusion of I^{131} throughout experiments, up to but not exceeding three hours in duration, resulted in essentially constant plasma counting rates.[5] Analyses for protein- bound I^{131} were performed in representative cases. The maximum amount of protein-bound I^{131} was observed during the last clearance period in a hyperthyroid patient and was equal to 1.7 per cent of total radio-iodine. In the majority of instances, no protein-binding of infused I^{131} was detected at the conclusion of clearance measurements.

II. *I^{131} clearance as a function of inulin clearance in the steady state*

In Figure 1 the clearance of I^{131} has been plotted against the concurrent value for the clearance of inulin for 40 studies on 34 euthyroid subjects (27 of whom had normal renal function and seven of whom had renal disease) and 11 studies on patients with thyroid dysfunction. All patients had essentially stable filtration rates during the periods of study. The range of glomerular filtration rates for the entire group was from 9 to 155 cc. per min. per 1.73 sq. m. The regression line drawn through the points was derived by the least squares method. The correlation coefficient is 0.82 and the P value less than 0.01, thereby indicating a strong relationship between $C_{I^{131}}$ and C_{In} for group data.

The validity of treating the subjects with normal thyroid function and those with thyroid dysfunction as members of the same population is

tion; 3) treatment of reagent blanks and standards identically with the unknowns; and 4) a wave length of 510 mμ on the Coleman Model 6A Spectrophotometer.

[5] Counting rates ranged from 37.2 to 202.7 cts. per sec. per 2 cc. of plasma. The range for individual subjects $\left(\frac{\text{High} - \text{Low}}{\text{High}} \times 100\right)$ varied from zero to 10 per cent with an average of 4.9 per cent for the group.

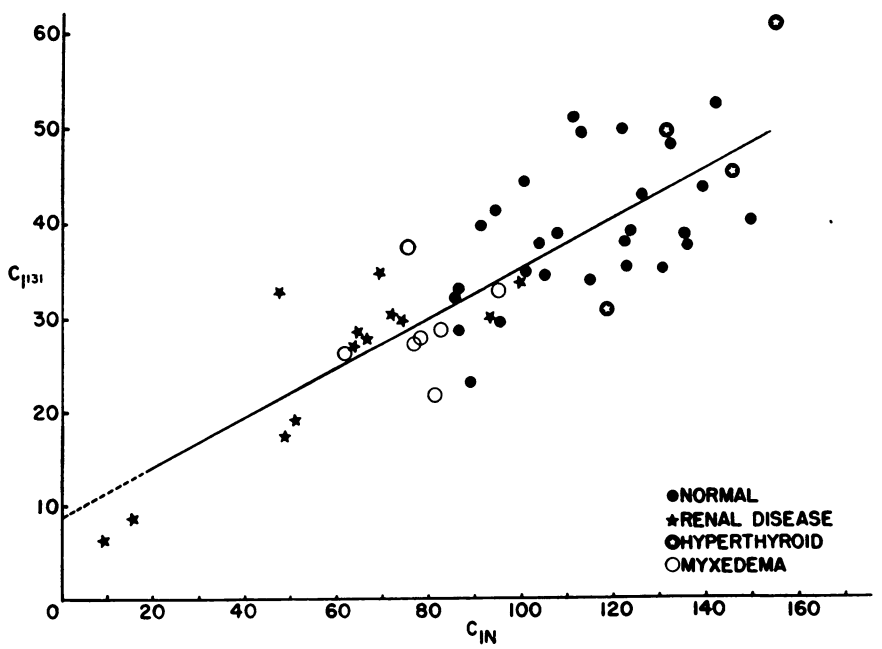

FIG. 1. RELATIONSHIP BETWEEN $C_{I^{131}}$ AND C_{In}

Each point represents the mean value of at least three separate clearance periods. Values are in cc. per min.

based upon a previous observation that a separate plot of $C_{I^{131}}$ *vs.* C_{in} for the present hyperthyroid and myxedematous patients was linear and could not be differentiated statistically from the same plot for euthyroid subjects (6). The equation derived for the combined data of Figure 1 is: $C_{I^{131}} = .268\ C_{in} + 8.6$.

III. *$C_{I^{131}}$ in the presence of acute alterations of glomerular filtration rate*

The linearity noted between glomerular filtration rate and I^{131} clearance in the group plot of patients with stable renal hemodynamics has been tested in individual subjects during acute increases and decreases in GFR.

A. *Acute increases in GFR:* In five subjects, C_{in} was acutely increased by the intravenous administration of Aminophylline. After three control periods, 0.25 to 0.50 gm. of Aminophylline was administered over a 5 to 10-minute period by single intravenous injection and a 10 to 15-minute period was allowed to compensate for delay time. Thereafter from three to five successive clearance periods were obtained. The response in all subjects was qualitatively the same and a representative experiment is recorded in Figure 2. A slight decrease was frequently noted in I^{131} plasma levels following Aminophylline administration; however, in no case did this decrease compensate for the elevation of GFR. Consequently, filtered load of I^{131} invariably rose. In each experiment, the percentage increase in C_{in} was associated with a greater percentage rise in $C_{I^{131}}$ such that the clearance ratios (C_I/C_{in}) consistently increased. Changes in C_{Cl}/C_{in} and C_{Na}/C_{in} were in the same direction as the change for C_I/C_{in}. Values for C_K/C_{in} did not follow a characteristic pattern. C_{PAH} increased slightly in four of the five experiments, but the rise was always less than that of C_{in}. Urine flow increased sharply immediately after injection but the increases were transient and values returned toward control levels after two or three clearance periods.

B. *Acute decreases in GFR:* Acute decreases in glomerular filtration rate were observed in five studies on four patients exhibiting transient peripheral vascular collapse during clearance measurements. One patient had orthostatic hy-

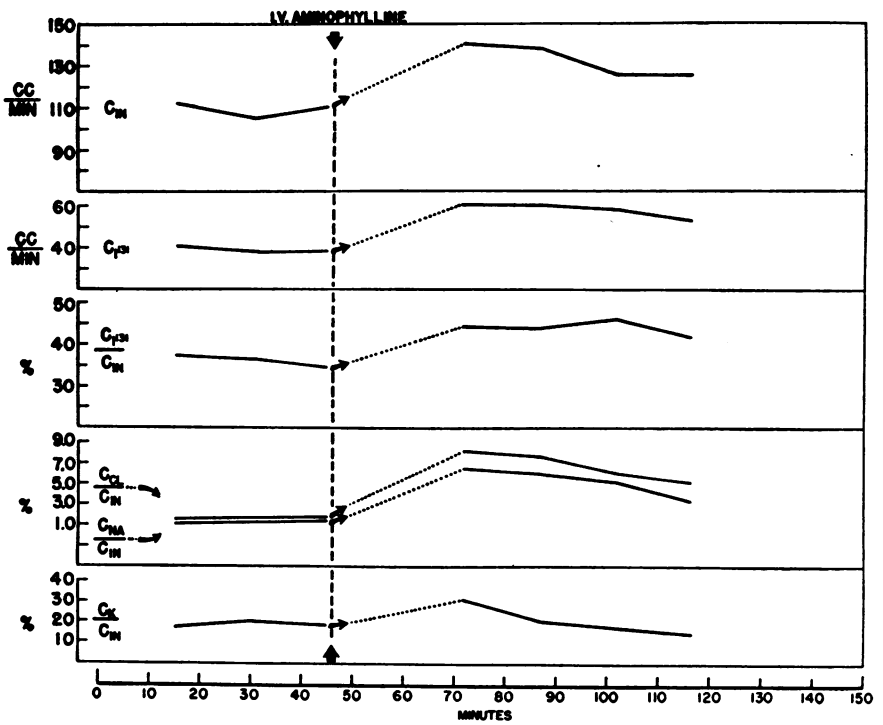

FIG. 2. EFFECTS OF ACUTE CHANGES IN GLOMERULAR FILTRATION RATE
Dotted line represents break for delay period.

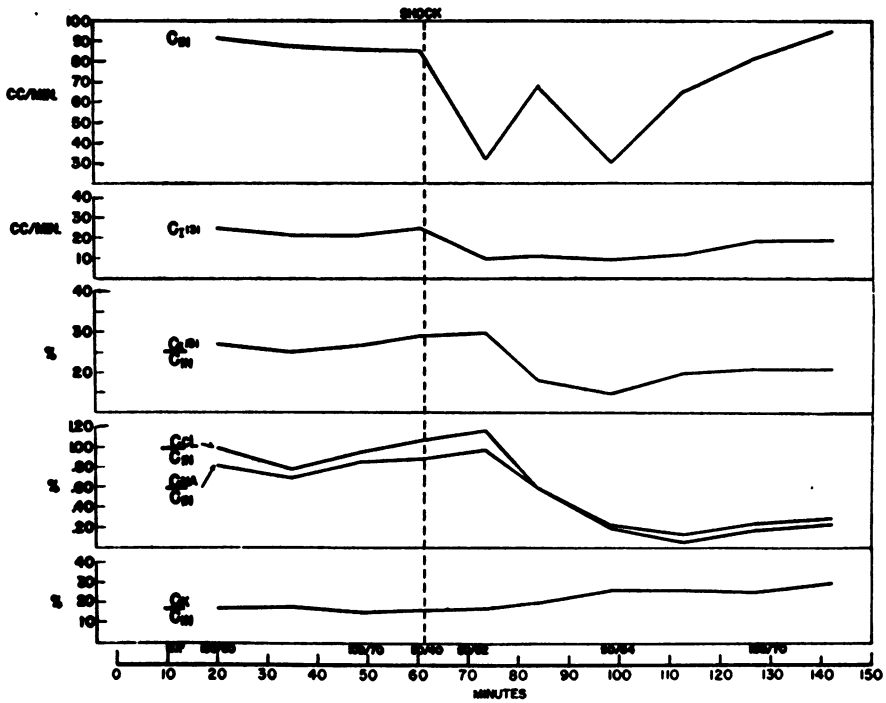

FIG. 3. EFFECTS OF ACUTE CHANGES IN GLOMERULAR FILTRATION RATE

potension and the fall in GFR was induced by elevation of the patient on a tilt table from zero to 90°. The other three patients (one of whom was studied twice) exhibited sudden onset of hypotension and bradycardia without apparent cause, and at different chronologic points in clearance measurements. In each instance, the hypotension was reversible without specific therapy.

Results of a representative experiment from this group are shown in Figure 3. In the first period after the onset of hypotension, inulin clearance decreased precipitously and was associated with a simultaneous proportional reduction in $C_{I^{131}}$. After this lag period, which was uniformly noted and may have been attributable to increased delay time in the nephra, $C_{I^{131}}$ decreased out of proportion to C_{in}. The changes for sodium and chloride were in the same direction as those for iodide; however, when C_I/C_{in} had returned toward normal, C_{Na}/C_{in} and C_{Cl}/C_{in} were still well below control levels. Changes for potassium were more variable than those of the other electrolytes and the results were inconclusive. C_{PAH} fell in all studies and in four the decreases were out of proportion to C_{in}, resulting in a fall in filtration fractions. Urine flow values fell in all instances and generally remained depressed after C_{in} had returned toward control levels.

IV. *Iodide loading*

The effects of acute loading with stable inorganic iodide were observed in five studies on four euthyroid patients. In two experiments, the patients were loaded chronically for one week prior to acute loading. After three control clearance periods in all patients, 0.5 gm. of NaI was administered by single intravenous injection, and 0.5 gm. was added to the sustaining infusion and delivered at a constant rate throughout the duration of the study. It was estimated that the amount of iodide administered increased the plasma inorganic iodide levels at least one thousand times.[6] A delay period of 10 to 15 minutes was allowed between completion of the priming injection of iodide and resumption of clearance measurements. Data from these studies are summarized in Table I, cases 1 to 5.

[6] This calculated value is based upon an assumed initial plasma inorganic iodide level of 1.0 μg per cent, and a maximal volume of distribution of inorganic iodide of 40 per cent of body weight.

TABLE I

The effects of acute and chronic iodide loading on renal hemodynamics, $C_{I^{131}}$, C_I/C_{in}, C_{Na}/C_{in}, C_{Cl}/C_{in}, and C_K/C_{in}

Case		C_{in}* cc./min.	$C_{I^{131}}$* cc./min.	C_I/C_{in} %	C_{PAH}* cc./min.	F.F. %	C_{Na}/C_{in} %	C_{Cl}/C_{in} %	C_K/C_{in} %
1	Control†	101	46	46	536	19	1.7	1.7	22
	Experimental	105	44	43	500	21	2.3	2.5	25
	% Change	+4	− 3	− 7	−7	+12	+31	+47	+14
2	Control	112	50	44	728	15	2.3		28
	Experimental	103	40	38	714	15	2.1		25
	% Change	−8	−21	−14	−2	± 0	− 6		− 9
3	Control	9.3	7.4	80	24	39	15	16	229
	Experimental	8.5	6.0	70	22	38	11	13	239
	% Change	−8	−18	−11	−7	− 2	−29	−23	+ 4
4	Control‡	113	46	41	514	22	1.7	1.9	24
	Experimental	115	46	41	525	22	2.6	2.7	23
	% Change	+1	± 0	± 0	+2	± 0	+53	+44	− 3
5	Control‡	107	34	32	661	16	1.7	1.8	21
	Experimental	108	32	30	676	16	1.5	1.7	17
	% Change	+1	− 4	− 5	+2	− 1	− 8	− 8	−19
	Mean change (1–5)	−2	− 9	− 8	−2	+ 1	+ 5	+15	− 2
6	Control§	108	39	36	510	21	1.3	1.6	18
	Experimental	113	46	41	514	22	1.7	1.9	24
	% Change	+5	+18	+13	+1	+ 4	+30	+20	+31

* Values corrected to 1.73 sq. m. body surface area.
† Control value in all studies is the mean of at least three clearance periods prior to drug administration. Experimental value is the mean of at least three clearance periods subsequent to drug administration. Calculations of *% change* were performed prior to rounding numbers off.
‡ Acute loading superimposed on chronic loading.
§ Chronic loading study.

Subsequent to acute iodide loading, $C_{I^{131}}$ decreased in four experiments (varying from 3 per cent to 21 per cent) and in one case remained unchanged. Values for C_I/C_{in} also decreased in four experiments but the range was only from 5 to 14 per cent. Mean decreases for the group were: C_{in}, 2 per cent, $C_{I^{131}}$, 9 per cent, and C_I/C_{in}, 8 per cent. The data from the two patients receiving acute iodide loading superimposed upon chronic loading (cases 4 and 5, Table I) do not appear to differ materially from those who received only the acute loading dose. In one patient (case 6, Table I) studies were performed before and after a five-day period of oral administration of a saturated solution of potassium iodide in the following stepwise daily doses: 5, 6, 7, 8, and 30 drops. Comparison of post-loading data with control values shows a slight increase in C_{in} (5 per cent) and a moderate rise in $C_{I^{131}}$ (18 per cent). The I^{131}/inulin clearance ratio increased 13 per cent.

V. *Thiocyanate data*

Clearance measurements were performed on five subjects receiving intravenous sodium thiocyanate in amounts varying from 475 to 900 mg. of thiocyanate ion. Plasma thiocyanate levels for the group varied from 3 mg. per cent to approximately 6 mg. per cent with the level remaining relatively stable in individual patients. Diagnosis and mean data before and after thiocyanate administration for each case are shown in Table II. The effects upon renal function were qualitatively the same in all subjects regardless of the diagnosis. In the majority of cases, filtration rate exhibited a slight decrease after injection. The mean decrease for all cases was 5 per cent. Similarly, PAH clearance showed a net decrease of 5 per cent after thiocyanate. The change in the I^{131}/inulin clearance ratios varied somewhat from case to case, both in direction and magnitude. None of the individual changes, however, was marked and

TABLE II

The effects of intravenous sodium thiocyanate on renal hemodynamics, C_I/C_{in}, C_{Na}/C_{in}, C_{Cl}/C_{in}, and C_K/C_{in}

Case		Diagnosis†	P_{SCN}‡ mg. %	C_{in}* cc./min.	C_{PAH}* cc./min.	C_I/C_{in} %	C_{Na}/C_{in} %	C_{Cl}/C_{in} %	C_K/C_{in} %
1	Control§	Eut. norm.	0.0	135	670	30	1.4	1.7	20
	Experimental		3.0	134	684	29	1.5	2.0	20
	% Change			− 1	+ 2	− 5	+ 8	+16	± 0
2	Control	Eut. norm.	0.0	91	559	43	2.2	2.2	
	Experimental		4.5	82	510	46	1.9	1.8	
	% Change			−10	− 9	+ 8	−17	−20	
3	Control	Myx-P	0.0	83	476	35	1.0	1.0	20
	Experimental		3.4	75	400	37	1.2	1.1	20
	% Change			− 9	−16	+ 5	+11	+ 9	± 0
4	Control	Hyp.	0.0	119	548	26	1.1	1.6	19
	Experimental		5.0	121	575	28	1.4	1.9	24
	% Change			+ 2	+ 5	+ 6	+23	+18	+24
5	Control	Hyp.	0.0	155	847	40	0.7	1.2	20
	Experimental		6.0	149	783	35	1.1	1.3	15
	% Change			− 4	− 8	−11	+53	+10	−28
Mean % Change				− 5	− 5	+ 1	+16	+ 6.0	− 1

* Values corrected to 1.73 sq. m. body surface area.
† Eut. norm. = euthyroid subject with normal renal function. Myx-P = primary myxedema. Hyp. = hyperthyroid.
‡ P_{SCN} = plasma thiocyanate levels.
§ Control and experimental as in Table I. Calculations of *% change* were performed prior to rounding numbers off.

the net change for the group was approximately zero. In general, sodium and chloride excretion rates increased after the administration of thiocyanate ion whereas changes in potassium excretion rates were variable. Following thiocyanate administration, plasma levels of I^{131} increased markedly in both hyperthyroid patients and moderately in one euthyroid subject. They remained unaltered in the myxedematous patient and the second euthyroid subject.

VI. *PAH loading data*

Eight patients were included in this group. After control periods, from 60 to 70 cc. of a 20 per cent solution of Na PAH was administered intravenously as a priming solution and the sustaining infusion was calculated to maintain plasma levels at approximately 60 mg. per cent. A period of 45 minutes was allowed for equilibration of plasma levels. Diagnosis and mean clearance values for each case are reproduced in Table III.

Glomerular filtration rates for this group ranged from 49 to 139 cc. per min. In six of the eight cases, filtration rates decreased following PAH loading, (from one to 15 per cent). In seven of the eight cases, the I^{131}/inulin clearance ratios rose. Although the magnitude of the ratio changes was variable, the mean increase for the group was 10 per cent. Sodium/inulin clearance ratios rose in all instances and the mean increase for the group was 291 per cent. Individual responses for chloride and potassium varied; however, the mean changes for both were positive. Thus, chloride/inulin clearance ratios increased 55 per cent, and potassium/inulin clearance ratios increased 30 per cent.

VII. *Mercurial diuretic data*

The effects of intravenous mercurial diuretics were studied in three euthyroid normal subjects. Details of one of these studies are shown graphically in Figure 4. This patient received 2 cc. of Thiomerin® by single intravenous injection over a 10-minute period. Filtration rate declined approximately 15 per cent from control levels subsequent to drug administration and remained relatively constant at the new level. Sodium and chloride excretion rates rose progressively following drug administration. Potassium excretion rate remained relatively stable. I^{131}/inulin clearance ratios showed a tendency to decrease during the 3rd to 5th clearance periods following injec-

TABLE III

The effects of PAH loading on C_{in}, C_I/C_{in}, C_{Na}/C_{in}, C_{Cl}/C_{in}, and C_K/C_{in}

Case		Diagnosis*	C_{in}† cc./min.	C_I/C_{in} %	C_{Na}/C_{in} %	C_{Cl}/C_{in} %	C_K/C_{in} %
1	Control	Eut. norm.	131	38	1.2	1.5	30
	Experimental		131	38	4.0	1.3	26
	% Change‡		0	± 0	+236	− 10	− 14
2	Control	Eut. norm.	139	32	1.7	1.8	24
	Experimental		123	33	4.9	1.7	20
	% Change		−12	+ 3	+187	−5	− 16
3	Control	Eut-RD	74	42	1.5	1.5	30
	Experimental		70	43	5.4	1.6	34
	% Change		− 5	+ 3	+252	+5	+ 13
4	Control	Eut-RD	94	33	1.4	1.3	20
	Experimental		80	40	5.7	1.7	28
	% Change		−15	+22	+308	+ 31	+ 39
5	Control	Eut-RD	49	36	2.1	2.2	22
	Experimental		45	42	6.6	2.9	25
	% Change		− 7	+15	+224	+ 31	+ 16
6	Control	Eut-RD	100	35	0.9	0.7	9
	Experimental		90	39	5.2	0.9	19
	% Change		−10	+12	+452	+ 42	+102
7	Control	Eut-RD	66	43	3.4	2.9	48
	Experimental		65	46	6.9	2.6	35
	% Change		− 1	+ 7	+105	− 12	− 28
8	Control	Eut-RD	65	45	1.3	1.11	29
	Experimental		70	53	8.9	5.09	65
	% Change		+ 8	+19	+563	+359	+125
Mean % Change			− 5	+10	+291	+ 55	+ 30

* Eut-RD = euthyroid patient with renal disease. Other definitions as in preceding tables.
† Values corrected to 1.73 sq. m. body surface area.
‡ Calculations of *% change* were performed prior to rounding numbers off.

tion of the mercurial. Urine flow values rose only during the last two periods of observation. Results in the other two cases were similar except that, 1) GFR did not drop, and 2) values for C_I/C_{in} remained essentially stable.

VIII. *The influence of the excretion of other electrolytes upon $C_{I^{131}}$*

In Figure 5 $C_{I^{131}}$ is plotted against the concurrent values for the clearance of sodium. Plots of C_{Cl} *vs.* $C_{I^{131}}$ and C_K *vs.* $C_{I^{131}}$ are qualitatively the same as that shown for C_{Na} *vs.* $C_{I^{131}}$. Although a rough correlation exists in the group data between $C_{I^{131}}$ and the clearances of the other electrolytes, the relationships are thought to represent an interdependence of each of the variables upon inulin clearance.

Experiments performed in the presence of acute changes of excretion rates of Na, Cl, and K have failed to show changes in $C_{I^{131}}$ which completely parallel any of the former ions. In a group of subjects with pulmonary tuberculosis, it has been noted that following peritoneal puncture with or without induction of pneumoperitoneum, excretion rates of sodium, chloride, and potassium decreased significantly (12). Values for the clearance of iodide, simultaneously determined, were variable and in several patients in whom marked decreases in excretion rates of other electrolytes occurred, iodide clearance was either unchanged or decreased only slightly. A representative study is shown in Figure 6. Other examples of an apparent dissociation of $C_{I^{131}}$ from the excretion of other electrolytes may be seen in the above noted experiments employing mercurial diuretics (Figure 4), PAH loading (Table III), and NaSCN administration (Table II).

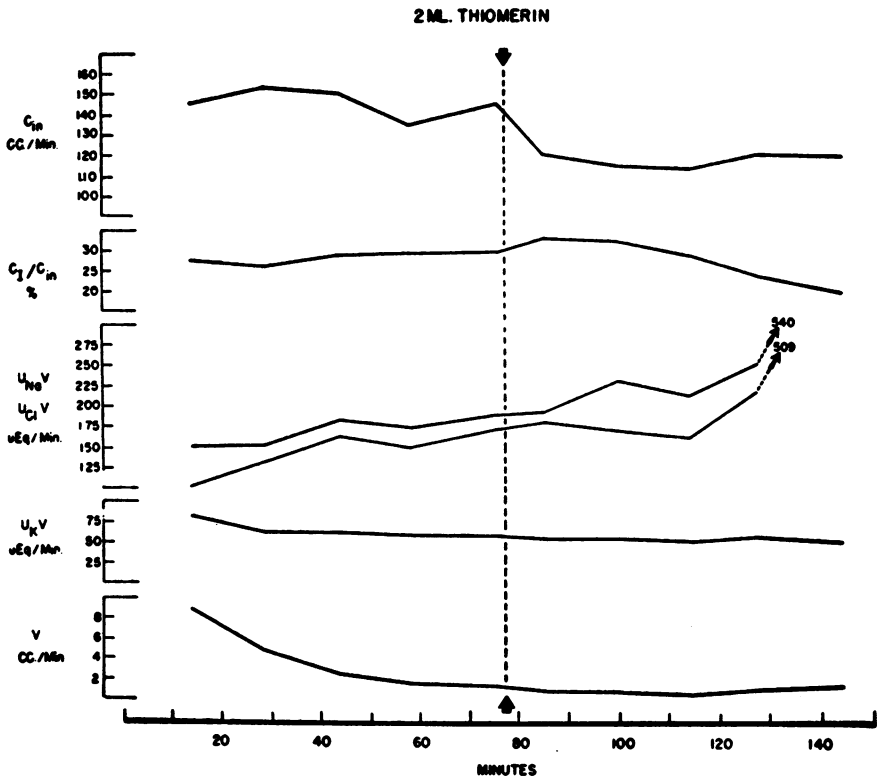

FIG. 4. INTRAVENOUS EFFECTS OF MERCURIAL DIURETICS

$U_{electrolyte}$ V = minute rate of excretion of designated electrolyte.

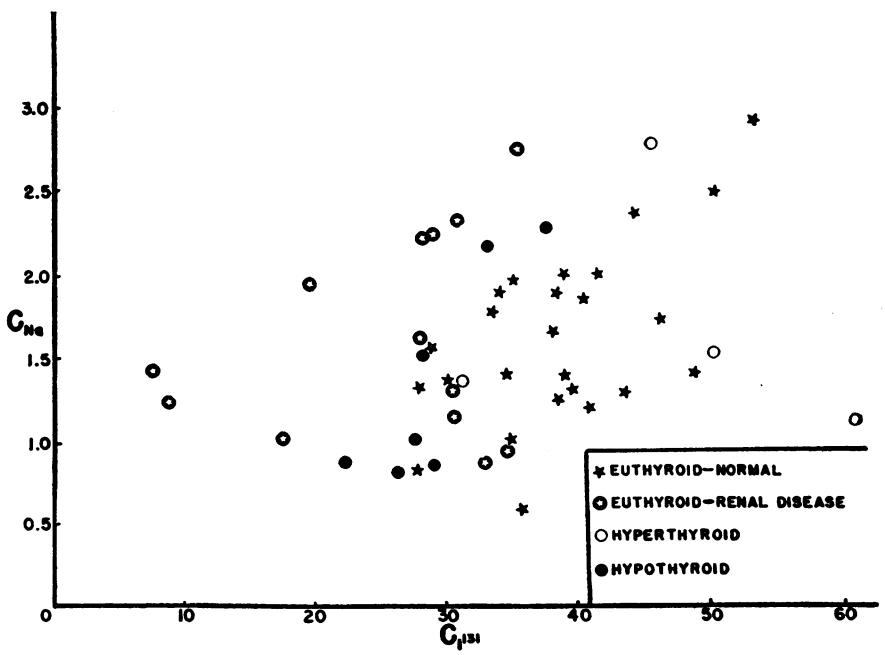

FIG. 5. RELATIONSHIP BETWEEN C_{Na} AND $C_{I^{131}}$

See legend Figure 1.

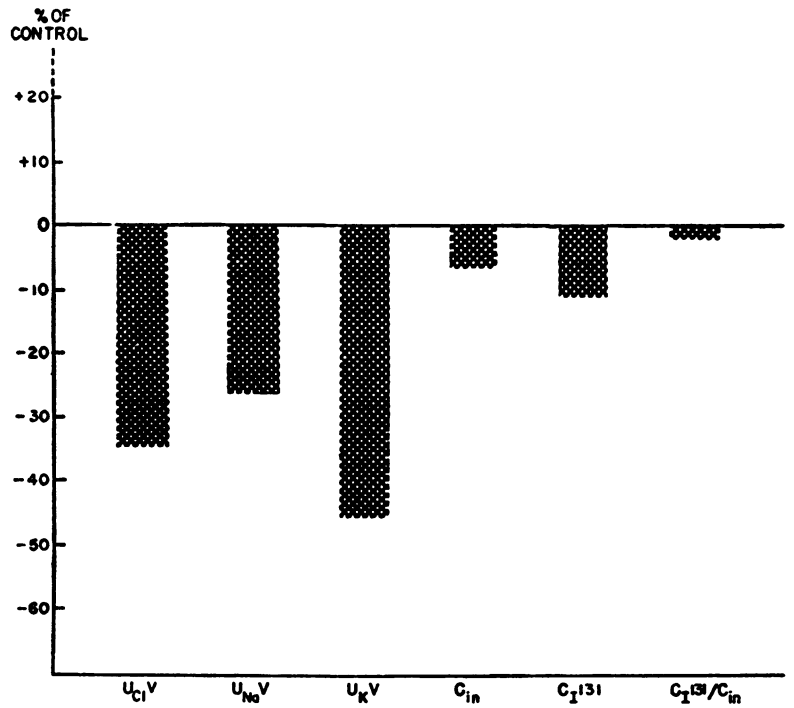

FIG. 6. EFFECTS OF INTRAPERITONEAL AIR INJECTION ON ELECTROLYTE CLEARANCE
See legend Figure 1.

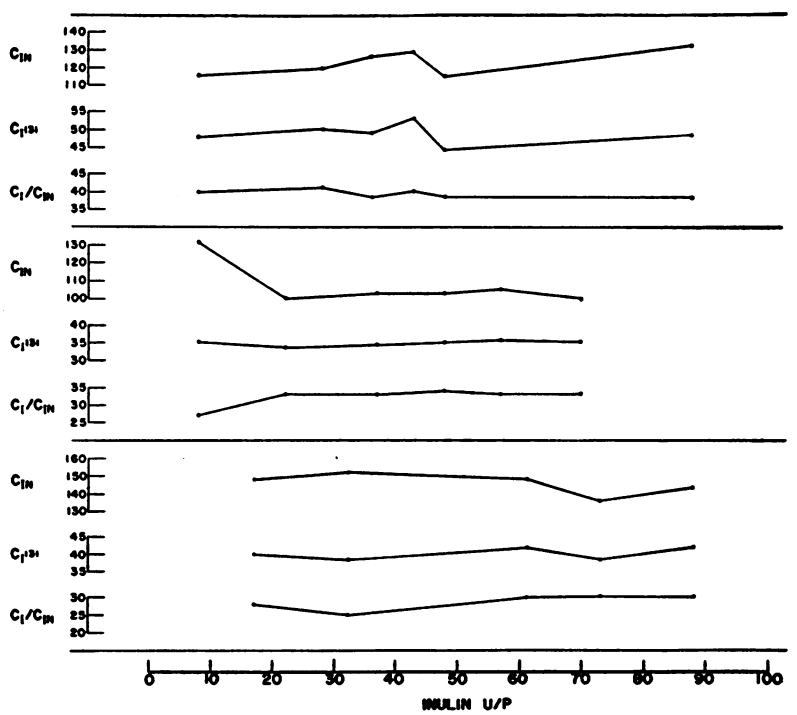

FIG. 7. EFFECTS OF DECREASING URINE FLOW
See legend Figure 1.

IX. *Urine flow*

Data for urine flow experiments were obtained from patients with normal renal function, having a range of glomerular filtration rates from 90 to 153 cc. per min. per 1.73 sq. m. Experiments performed on three individual patients in the presence of decreasing rates of urine flow are shown in Figure 7. In each instance $C_{I^{131}}$, C_{in}, and the I^{131}/inulin clearance ratio are plotted against the urine/plasma (U/P) ratio for inulin. The latter is employed as a measure of the degree to which the glomerular filtrate has been concentrated by the reabsorption of water. The total range of U/P values for the three patients was from 9 to 90. In none of the cases did I^{131}/inulin clearance ratios decrease with increasing U/P values.

Consecutive individual clearance periods obtained during constant or falling urine flows (increasing U/P values) were available in 16 studies on patients with normal filtration rates. Of these, 10 cases (including the three shown in Figure 7) had variable or no changes in I^{131}/inulin clearance ratios, four had decreasing I^{131}/inulin clearance ratios, and two had increasing I^{131}/inulin clearance ratios. When the I^{131}/inulin clearance ratios for these subjects are plotted against the inulin U/P ratios (circles in Figure 8), there is a suggestion of a slight tendency for clearance ratios to decrease with increasing U/P values.

The effects upon I^{131}/inulin clearance ratios of increasing rates of urine flow, measured during the ascending limb of water diuresis, are represented for an individual case in Figure 9. The first six clearance periods cover a range of urine flows from 0.7 to 5.8 cc. per min. per 1.73 sq. m., and a range of inulin U/P ratios from 190 to 20. The results fail to show a rise in I^{131}/inulin clearance ratios with falling U/P values, and in fact a slight decrease in C_I/C_{in} values occurred. With the onset of decreasing rates of urine flow (increasing inulin U/P values), clearance ratios remained essentially constant.

Consecutive individual clearance periods obtained during rising urine flows were available in 10 subjects with normal renal function. Examination of these data showed no consistent change in I^{131}/inulin clearance ratios with falling inulin U/P values.

X. *Osmotic diuresis*

The behavior of $C_{I^{131}}$ has been investigated in the presence of osmotic diuresis associated with mannitol loading and spontaneous osmotic diuresis in patients with renal disease.

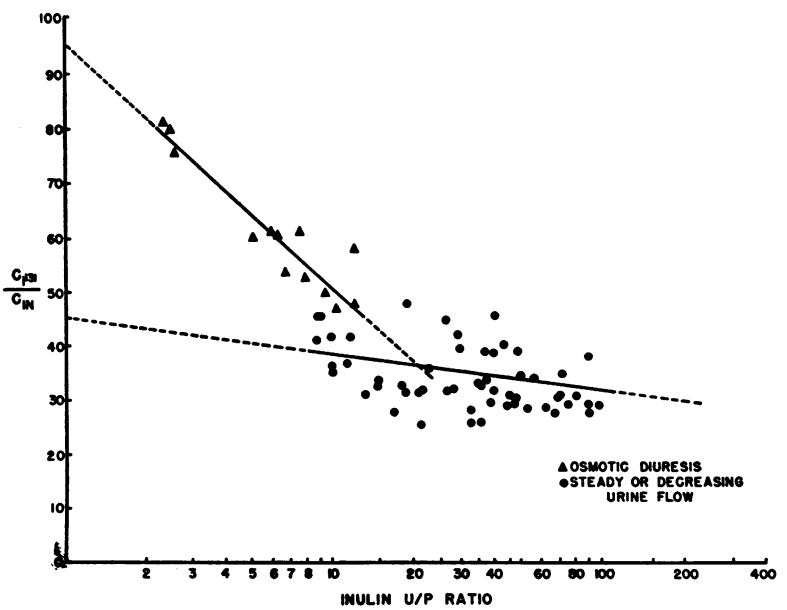

FIG. 8. RELATIONSHIP BETWEEN I^{131}/INULIN CLEARANCE RATIO AND INULIN U/P RATIO

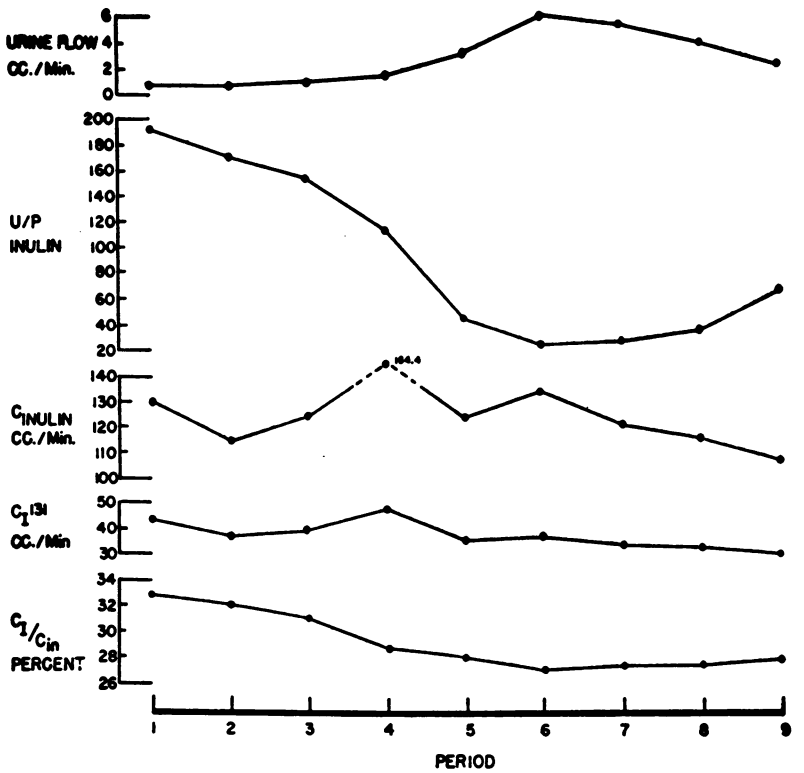

FIG. 9. EFFECTS OF INCREASING URINE FLOW ON $C_{I^{131}}$

A. *Mannitol diuresis:* Two patients were studied during intravenous mannitol loading. The first case is shown in Table IV. Glomerular filtration rate remained relatively stable throughout the period of study. Inulin U/P ratios decreased from 20 to a minimum of 5. I^{131}/inulin clearance ratios rose from 31 per cent to 60 per cent and urea/inulin clearance ratios rose from 47 per cent to 77 per cent. The percentage of filtered water excreted increased from 5.7 to 22.

In the second patient subjected to mannitol diuresis the results were comparable to the above study. Inulin U/P values decreased from a maximum control value of 40 to a minimum of 7.8 and I^{131}/inulin clearance ratios increased from 32 to 53 per cent. The percentage of filtered water excreted increased from 2.7 to 14.

B. *Osmotic diuresis associated with renal disease:* Two patients with chronic glomerulonephritis, both with inulin U/P ratios below eight

TABLE IV

Osmotic diuresis after mannitol loading

Period	Time *min.*	V* *cc./min.*	U/P†	C_{in}‡ *cc./min.*	C_I/C_{in} %	C_{urea}/C_{in} %	V/wC_{in}§ %
1	0–16	5.3	18.8	99	31	47	5.8
2	16–29	5.2	17.8	93	33	47	6.1
3	29–41	4.4	21.1	93	32	46	5.2
Mannitol							
4	41–57	4.7	19.6	92	35	49	5.6
5	57–71	8.0	10.1	81	47	67	10.8
6	71–81	12.7	6.5	83	54	69	16.6
7	81–91	16.7	4.9	82	60	77	22.0

* V = urine flow.
† U/P = urine/plasma inulin ratio.
‡ Values corrected to 1.73 sq. m. body surface area.
§ Percentage of filtered water excreted was computed from the conventional formula V/wC_{in}, where V is the true urine flow, C_{in} is the filtration rate, and w is the correction for water content of plasma.

were studied. The first patient had a glomerular filtration rate of 9.3 cc. per min. per 1.73 sq. m. and a mean inulin U/P value of 2.4. The I^{131}/inulin clearance ratios averaged 80 per cent in this subject as opposed to the range of 26 to 51 per cent observed in 50 studies on patients with U/P ratios greater than 8. The second patient with chronic glomerulonephritis had an inulin U/P value of 4.4 and an I^{131}/inulin clearance ratio of 58 per cent.

Data were obtained from one patient with salt-losing nephritis. At the time of clearance measurements this subject was excreting from 13 to 15 per cent of his filtered load of sodium and the average rate of excretion of sodium was 1 mEq. per min. Inulin U/P ratios ranged from 6.5 to 8.7 and the I^{131}/inulin clearance ratios averaged 61 per cent.

DISCUSSION

Two general categories of data have been obtained in the present studies: a) *Group data* from individual subjects presumably in a steady state; and b) *Data from individual subjects,* each serving as his own control, in whom experimental conditions were acutely altered. The group data supply general information which is representative of the population. The individual studies allow for an examination of certain of the dynamic aspects of iodide excretion.

In the group data, a linear relationship between $C_{I^{131}}$ and C_{in} is apparent over a range of filtration rates from 40 to 155 cc. per min. Moreover, the values for $C_{I^{131}}$ were invariably less than the concurrent values for C_{in}. These observations imply that: a) $C_{I^{131}}$ is filtration dependent; and b) based on the assumption that plasma iodide is largely or completely filtered at the glomerulus, some of the filtered iodide ion is reabsorbed from the tubular urine. The nature of the tubular transport mechanism is not apparent in the group data and the individual studies include a series of experiments designed to elucidate the properties of this mechanism.

The filtration dependence of $C_{I^{131}}$ was examined in the presence of acute alterations of glomerular filtration rate. Acute increases or decreases in GFR were always accompanied by changes in $C_{I^{131}}$ which were in the same direction, but proportionately greater than those of C_{in}. I^{131}/inulin clearance ratios thus increased with rising filtration rates and decreased with falling filtration rates. It is well known that sudden alterations in filtration rate produce striking changes in electrolyte excretion. Such changes are presumably related to the creation of a glomerulo-tubular imbalance and with respect to the present study do not appear to offer direct information regarding the mechanism of the tubular transport of iodide. The possibility that Aminophylline, which was employed to increase GFR, specifically blocked the tubular reabsorption of iodide cannot be evaluated on the basis of existing information.

In contrast to the effects of elevating the filtered load of iodide by increasing GFR, elevation of filtered load through administration of an amount of stable iodide calculated to raise plasma I^{127} levels over a thousand-fold resulted in only a slight and inconsistent decrease in iodide/inulin clearance ratios. It is not yet clear whether this decrease is due to: 1) analytic error; 2) a change in the experimental conditions (*e.g.,* failure of equilibration of loading doses with the iodide, pool, decrease in filterability of iodide, *etc.*); or 3) a minor alteration in the transport of iodide relative to the filtered load. In any event, the data indicate that with large increases in plasma iodide concentrations, the rate of urinary excretion of inorganic iodide remains essentially proportional to plasma iodide levels. Reabsorption, therefore, must also remain proportional to plasma iodide levels. The relative independence between $C_{I^{131}}$ and plasma iodide levels, which has previously been noted by Childs, Keating, Rall, Williams, and Power (2), is more suggestive of passive reabsorption of iodide as a consequence of a concentration gradient between tubular urine and plasma than it is of active reabsorption. Thus, the clearance of a substance excreted by physical processes alone is essentially independent of plasma levels, whereas the clearance of a substance transported by an active reabsorptive mechanism is influenced in a characteristic manner by elevation of plasma levels beyond a critical point. It is quite possible that the present loading experiments did not elevate plasma iodide levels sufficiently high to demonstrate an iodide Tm, for despite a thousand-fold increase in plasma iodide concentrations, the latter were still present in micro quantities. If a transport maximum for iodide does exist, it

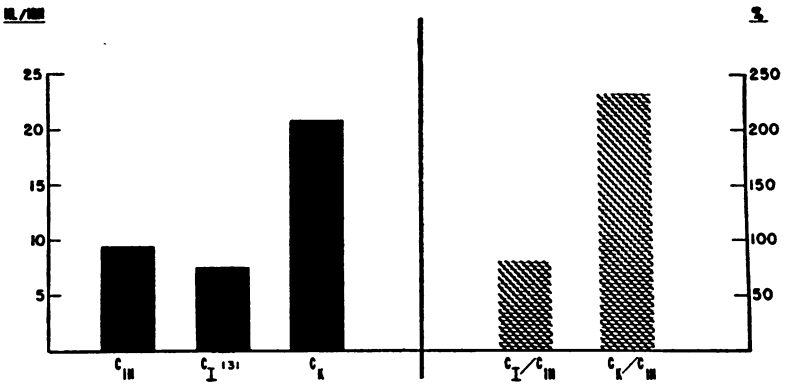

FIG. 10. THE CLEARANCE OF I^{131} IN A PATIENT WITH DEMONSTRABLE POTASSIUM SECRETION

must be geared to an iodide level far in excess of the physiologic range and it may not be possible to demonstrate its presence in humans without administration of toxic doses of iodide.

The data on iodide loading may also be examined from the point of view of evaluating iodide secretion. In studies of potassium excretion, loading with potassium salts has frequently been found to induce demonstrable secretion of potassium (13). Moreover, chronic loading with potassium facilitates the excretion of sudden large loads at more rapid rates and frequently elevates the clearance of potassium above that of inulin (13). In the present studies not only did C_I/C_{In} values not rise above unity after acute loading, but clearance ratios appeared to decrease slightly. In addition, chronic loading in two cases did not facilitate the excretion of sudden acute loads. In a subject with chronic renal disease, the opportunity to study iodide clearance in the presence of demonstrable K secretion was afforded (Figure 10). The potassium/inulin clearance ratio was 229 per cent, whereas the iodide/inulin clearance ratio was 79 per cent. Acute iodide loading in this patient resulted in a decrease in I^{131}/inulin clearance ratio to 70 per cent, rather than in an increase to a level exceeding unity. Thus, neither in this patient nor in any other subject studied to date has the value for $C_{I^{131}}$ exceeded that for C_{In}.

Thiocyanate ion has long been known to block the ability of the thyroid gland to trap inorganic iodide. Recently, it has been shown that thiocyanate also exhibits a rapid and definite blocking action on the iodide concentrating processes of the salivary gland (14, 15), although chloride secretion is apparently unaffected. Gastric secretion has also been altered by thiocyanate (16). Finally, increases in urinary chloride have been observed after thiocyanate administration (17), and a significant sodium diuresis has been reported following oral doses of thiocyanate ion (18). On the basis of these facts, it might be anticipated that thiocyanate should influence the renal excretion of iodide if an active mechanism is responsible for the tubular transport of this ion.

That the plasma concentrations of thiocyanate ion in the present patients were biologically active is suggested by the following: 1) In one subject salivary/plasma iodide ratios were measured before and after thiocyanate administration. The values for this ratio decreased 63 per cent and 53 per cent from control levels during the first and third clearance periods, respectively, after the administration of thiocyanate. 2) Plasma concentrations of I^{131} increased sharply in the two hyperthyroid patients and moderately in one of the two euthyroid subjects after NaSCN administration. These changes occurred during the infusion of I^{131} at a constant rate and probably resulted from a decrease in the volume of distribution of I^{131} due to a blocking of the thyroidal iodide trapping mechanism. Consonant with this explanation is the fact that plasma I^{131} concentrations failed to rise after thiocyanate administration to the myxedematous patient. 3) Sodium and chloride excretion rates increased after thiocyanate administration in four of the five cases.

The failure to demonstrate a significant thiocyanate effect on the I^{131}/inulin clearance ratios suggests that iodide is not handled by an active

tubular transport mechanism that may be affected by the thiocyanate ion.

The experiments involving the intravenous administration of mercurial diuretics make it possible to study the variations in $C_{I^{131}}$ under the influence of an agent capable of blocking sodium and/or chloride reabsorption. In each of the cases reported, sodium and chloride excretion rates increased following mercurial administration; however, I^{131}/inulin clearance ratios remained constant in two cases and decreased in the third. Thus, mercurial diuretics in doses sufficient to invoke moderate natriuresis and chloruresis did not noticeably decrease the tubular reabsorption of iodide.

Comparison of the clearance of I^{131} to the clearance of other electrolytes suggests that the tubular transport of iodide is not identical to that of sodium, chloride, or potassium, all of which are governed by active transport mechanisms. Thus, 1) the clearance of I^{131} (in cc. per min) is greater than C_{Na}, C_{Cl}, and C_K; 2) $C_{I^{131}}$ bears only an incidental relationship to the concurrent values for the clearances of sodium, chloride, and potassium in group data; and, 3) in individual studies altering the excretion rates of sodium, chloride, and potassium acutely within a limited range by administration of PAH, NaSCN, and mercurial diuretics, and by peritoneal puncture has not induced proportional changes in $C_{I^{131}}$.

The studies relating $C_{I^{131}}$ to rates of urine flow when the latter are decreasing are equivocal, but suggest at most a very slight relationship. $C_{I^{131}}$ does not appear to be influenced by rising rates of urine flow.

The osmotic diuresis data indicate that the clearance of I^{131} approaches the glomerular filtration rate as the inulin U/P ratio approaches one. This relationship shown in Figure 8 suggests that the tubular reabsorption of iodide may be a function of the proximal tubular reabsorption of water.

Certain points of similarity appear between the clearance of I^{131} and that of urea, a substance thought by most observers to be reabsorbed by passive back-diffusion. The data of Chasis and Smith (19) show that above a C_{in} of 40, C_{urea} is approximately a linear function of GFR. Above this level of C_{in}, I^{131} clearance is also a linear function of C_{in}.[7] In addition, both the clearance of urea (within a limited range) and the clearance of I^{131} are essentially independent of their respective plasma levels. A further point of similarity between C_{urea} and $C_{I^{131}}$ is seen in osmotic diuresis studies. It has been noted that during osmotic diuresis in the dog (20), urea/inulin clearance ratios rise with decreasing inulin U/P ratios such that at an extrapolated inulin U/P value of one, urea/inulin clearance ratios approach 100 per cent. At an extrapolated inulin U/P ratio of one, I_{131}/inulin clearance ratios also approach 100 per cent.

The present studies bring to light at least one possible difference between the excretion patterns for iodide and that for urea. The clearance of urea is influenced in a definite and predictable manner by changing rates of urine flow. The influence of decreasing rates of urine flow on $C_{I^{131}}$ as has been mentioned, is equivocal. If any relationship exists, it is not of the same order of magnitude as that noted for urea in the studies of Shannon in dogs (20) or Chasis and Smith in humans (19). In the presence of rising urine flows, it is well established that urea/inulin clearance ratios demonstrate a spurious rise (*i.e.*, "exaltation"). The present data fail to reveal a similar rise for I^{131}/inulin clearance ratios. One possible explanation for the poor relationship between $C_{I^{131}}$ and urine flow is that the distal tubule and collecting ducts may be relatively impermeable to the back-diffusion of iodide.

The majority of the present data appear most readily explicable on the basis of passive back-diffusion of iodide from tubular urine to plasma as a function of a concentration gradient created by the reabsorption of water from the glomerular filtrate. The fact that the iodide ion, despite its presence in trace quantities, must still be viewed as a charged particle does not appear to preclude diffusion as the mechanism of reabsorption.

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[7] The linear correlation coefficient for the data of Chasis and Smith including all points where C_{in} exceeds 40 is 0.71 ($p = < .01$). The linear correlation coefficient for the present data is 0.82 ($p = < .01$). It must be noted that the urea data were obtained from subjects with glomerulonephritis, whereas the I^{131} data were obtained predominantly from patients without renal disease. This fact does not appear to invalidate the comparison.

SUMMARY AND CONCLUSIONS

1. The clearance of I^{131} has been determined (by constant infusion technique) simultaneously with other renal functions in an attempt to establish the mechanism of iodide excretion in the human kidney. Fifty-eight clearance studies were performed on 49 subjects with varying states of thyroid function and varying states of renal function.

2. In group data, $C_{I^{131}}$ has been noted to be a linear function of C_{in} over a wide range of filtration rates. Moreover, $C_{I^{131}}$ was always less than the concurrent value for C_{in}.

3. Acute increases and decreases in filtration rate were associated with changes of $C_{I^{131}}$ in the same direction as those of C_{in}, but these changes were always proportionately greater than those of GFR.

4. Increasing the filtered load of iodide by inorganic iodide loading resulted in slight decreases in I^{131}/inulin clearance ratios rather than; a) an increase in $C_{I^{131}}$ values asymptotically toward the concurrent values for C_{in} as might occur if a reabsorptive Tm had been surpassed, or b) an increase in I^{131}/inulin clearance ratios above unity as might occur if a tubular secretory mechanism existed.

5. The influence upon the renal clearance of I^{131} of agents capable of blocking renal tubular and/or iodide transport mechanisms has been investigated.

a) Sodium thiocyanate did not materially alter I^{131}/inulin clearance ratios, although plasma thiocyanate concentrations were adequate to alter plasma I^{131} levels and to change salivary/plasma I^{131} concentration ratios.

b) PAH loading was associated with slight increases in I^{131}/inulin clearance ratios in the presence of slight decreases in glomerular filtration rates. These alterations in the clearance ratios have been provisionally attributed to an osmotic diuretic effect of the loading agent.

c) Mercurial diuretics did not increase I^{131}/inulin clearance ratios despite a moderate natriuresis and chloruresis.

6. The clearance of I^{131} has been found to be essentially independent of the clearance of Na, Cl, and K in group data. In the presence of acute changes in excretion rates of Na, Cl, and K within limited ranges of the latter, $C_{I^{131}}$ exhibited only minor changes.

7. I^{131} clearance has been found to be influenced at most to a slight degree by decreasing rates of urine flow, over a range of inulin U/P values from 8 to 100 and apparently not at all by increasing rates of urine flow over a range of inulin U/P values from 190 to 11.

8. In the presence of osmotic diuresis, the I^{131}/inulin clearance ratios increased with decreasing inulin U/P values. At an extrapolated inulin U/P ratio of one, the I^{131}/inulin clearance ratio approached 100 per cent.

9. It is concluded on the basis of the present studies that iodide, in the human kidney, is filtered at the glomerulus and partially reabsorbed by the tubules. The data do not support the presence of an active tubular transport mechanism, and although this possibility cannot yet be excluded, it is provisionally held that iodide is reabsorbed predominantly by passive back-diffusion.

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REFERENCES

1. Keating, F. R., Jr., Power, M. H., Berkson, J., and Haines, S. F., The urinary excretion of radioiodine in various thyroid states. J. Clin. Invest., 1947, **26**, 1138.
2. Childs, D. S., Jr., Keating, F. R., Jr., Rall, J. E., Williams, M. D. D., and Power, M. H., The effect of varying quantities of inorganic iodide (carrier) on the urinary excretion and thyroidal accumulation of radioiodine in exophthalmic goiter. J. Clin. Invest., 1950, **29**, 726.
3. Myant, N. B., Pochin, E. E., and Goldie, E. A. G., The plasma iodide clearance rate of the human thyroid. Clin. Sc., 1949, **8**, 109.
4. McConahey, W. M., Keating, F. R., Jr., and Power, M. H., An estimation of the renal and extrarenal clearance of radioiodide in man. J. Clin. Invest., 1951, **30**, 778.
5. Berson, S. A., and Yalow, R. S., The effect of cortisone on the iodine accumulating function of the thyroid gland in euthyroid subjects. J. Clin. Endocrinol. & Metab., 1952, **12**, 407.
6. Hlad, C. J., Jr., and Bricker, N. S., Renal function and I^{131} clearance in hyperthyroidism and myxedema. J. Clin. Endocrinol. & Metab., 1954, **14**, 1539.

7. Riggs, D. S., Quantitative aspects of iodine metabolism in man. Pharmacol. Rev., 1952, **4**, 284.
8. Roe, J. H., Epstein, J. H., and Goldstein, N. P., A photometric method for the determination of inulin in plasma and urine. J. Biol. Chem., 1949, **178**, 839.
9. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B., and Graber, M., The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. J. Clin. Invest., 1945, **24**, 388.
10. Van Slyke, D. D., and Hiller, A., Application of Sendroy's iodometric chloride titration to protein-containing fluids. J. Biol. Chem., 1947, **167**, 107.
11. Gregersen, M. I., and Stewart, J. D., Simultaneous determination of the plasma volume with T-1824, and the "available fluid" volume with sodium thiocyanate. Am. J. Physiol., 1939, **125**, 142.
12. Bricker, N. S., and Gregory, L., The influence of peritoneal puncture, with and without pneumoperitoneum, on renal function and electrolyte excretion. Unpublished observations.
13. Berliner, R. W., Kennedy, T. J., Jr., and Hilton, J. G., Renal mechanisms for excretion of potassium. Am. J. Physiol., 1950, **162**, 348.
14. Myant, N. B., Corbett, B. D., Honour, A. J., and Pochin, E. E., Distribution of radioiodide in man. Clin. Sc., 1950, **9**, 405.
15. Freinkel, N., and Ingbar, S. H., Concentration gradients for inorganic I^{131} and chloride in mixed human saliva. J. Clin. Invest., 1953, **32**, 1077.
16. Davenport, H. W., The inhibition of carbonic anhydrase and of gastric acid secretion by thiocyanate. Am. J. Physiol., 1940, **129**, 505.
17. Rapoport, S., and West, C. D., Ionic antagonism: Effect of various anions on chloride excretion during osmotic diuresis in the dog. Am. J. Physiol., 1950, **162**, 668.
18. Pines, K. L., and Perera, G. A., Thiocyanate effect on sodium excretion in normotensive and hypertensive subjects. Proc. Soc. Exper. Biol. & Med., 1952, **81**, 149.
19. Chasis, H., and Smith, H. W., The excretion of urea in normal man and in subjects with glomerulonephritis. J. Clin. Invest., 1938, **17**, 347.
20. Shannon, J. A., Glomerular filtration and urea excretion in relation to urine flow in the dog. Am. J. Physiol., 1936, **117**, 206.