THE EFFECTS OF RENAL FAILURE AND CONGESTIVE HEART FAILURE ON THE URINARY EXCRETION AND THYROID UPTAKE OF I-131

A Thesis

Presented to

The University of Manitoba

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

---

by

John F. S. Hughes

September 1951

ACKNOWLEDGMENTS

I wish to thank Dr. W. F. Perry for valuable advice and criticism in the preparation of this thesis and also for his tutorage and guidance during my year in the Department of Physiology and Medical Research of the University of Manitoba.

I am indebted to the Staff Physicians of the Winnipeg General Hospital for permission to use their patients in this research study and to Dr. J. P. Gemmel for their care and management during this period.

I also wish to acknowledge Dr. Marion Ferguson for the sodium analyses used in this thesis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION AND REVIEW OF THE LITERATURE

The enigma of iodine metabolism has intrigued and perplexed biological scientists for centuries. As early as ancient Grecian times it was known that sponges and seaweed were efficacious in the treatment of goitre. Through the following centuries products of the sea were intermittently used in the treatment of enlarged thyroid glands with no idea of what was the effective component. In 1820, nine years after Courtois had discovered the element iodine, Coindet another Frenchman suggested that the beneficial effect on goitre of these marine products might be due to the iodine they contained (1). He put his hypothesis to the test and found that the administration of tincture of iodine to patients with goitre sometimes led to the disappearance of the goitre.

While physicians were thus experimenting on the therapeutic value of iodine in goitre, evidence of the connection between iodine deficiency and goitre was being accumulated by other observers. Angelini (1) in 1824 and Cantu (1) in 1825 found iodine in certain springs which had the reputation for the cure of goitre. In 1831 Boussingault (1) recorded that in the Andes, where goitre was prevalent, the sea salt of Guaca was used as a cure for goitre, and other districts in that region, where salt rich in iodine was in general use, were free from goitre. Probably as a result of

these observations Prevost (1) put forward the suggestion in 1849 that goitre was due to deficiency of iodine in drinking water. He suggested that the iodine naturally present in certain salts protected against the disease.

In 1895 Baumann discovered iodine in the thyroid gland (2). He also noted that the concentration of iodine in goitrous glands was considerably reduced. Following this discovery it became the opinion of most authorities that the efficacy of dried thyroid gland in the treatment of the myxoedematous patient was directly related to its iodine content. The position that iodine plays in thyroid function became clearer when Kendall isolated crystalline thyroxine and showed iodine to be an essential element in its constitution (3). Therefore it became apparent that iodine was essential for the proper funtioning of the thyroid gland.

From the early 1900's further progress in the study of iodine metabolism was hampered by the fact that iodine was present in the body in such minute amounts that the available biochemical methods of analysis of the day were not sufficiently accurate to obtain true values for iodine concentration in the body tissues. Therefore it is not surprising that there was very little agreement between investigators on the iodine content of the different body tissues. To add to this difficulty iodine intake varied immensely over the world; being highest in areas bordering the sea. As the intake of iodine above a certain minimum amount seemed to have no clinical effect upon thyroid function; and as the

iodine content of the blood and body tissues varied widely with iodine intake, it became apparent that all of this iodine was not combined in the form of physiologically active thyroxine. Eventually methods of analysis for organic plasma iodine were perfected which gave consistently good results (4). It was found that the amount of organic or protein-bound iodine in the plasma was raised in hyperfunction and lowered in hypofunction of the thyroid gland. Although this proved to be a good test for thyroid function, the method is analytically difficult and only practical in well equipped laboratories.

Maine and Feiss in 1915 showed, by means of perfusion experiments in dogs, that the thyroid has a selective affinity for iodine (5). It was not until 1927 however that Sturm made use of this information in studying iodine metabolism in thyroid disease. He found that after an oral dose of iodine patients with thyrotoxicosis excreted less of the dose than did normal subjects (6). Elmer in 1934 used a similar iodine tolerance test to study normal, hyperthyroid, and hypothyroid individuals (7). This test however was also inaccurate because of the inherent difficulty in analysing for relatively small amounts of iodine.

The basal metabolic rate has been and still is used frequently as a test of the thyroid function. However being a test of the body response to metabolic stimulants it is not specific to thyroid function.

Not until 1938 when Hertz, Roberts, and Evans first intro-

duced radioactive isotope technique into the study of thyroid physiology was there available an accurate and relatively easily performed test for the assessment of thyroid function (8). Since this time a large volume of information on the manner in which radio-iodide is handled by normal and by dysfunctioning thyroid glands has accumulated.

It has become established that radioactive iodine is handled chemically and physiologically in an identical manner to that of its stable isotope: provided that the resulting radiations are too small to result in any biologic changes (9). Therefore by studying the behavior of I-131 which can be measured accurately and easily it was possible to gain information on iodine metabolism which was previously unobtainable.

Early studies of thyroid function with radio-iodide were achieved by measuring the percentage urinary excretion of radio-iodide after the administration of a known amount of the isotope. This of course was an indirect method of estimating thyroid function but it was used because of the relative ease of examining urine for radio-iodide content. Before this method could be used to estimate thyroid iodine metabolism it had to be established that almost all of the administered radio-iodide was either taken up by the thyroid gland or excreted in the urine. Skanse was able to recover from the urine an average of 97.9% of the given dose of radio-iodide by 48 hours in 8 patients with total thyroidectomies (10). Hamilton and Soley were able to recover 98% of the administered dose of

radio-iodide from the examination of urine, faeces and excised thyroids (11). They showed that very little of the isotope was excreted in the faeces. Therefore it would seem that for practical purposes iodine is either taken up by the thyroid or excreted by the kidneys.

Somewhat later a direct in vivo method of measuring radioactivity in the thyroid gland was introduced by Hamilton and Soley (12). Such an in vivo method would appear to be superior to that using urine excretion values. However as thyroids vary so much in size it was necessary to set the counting tube at a considerable distance from the thyroid. This greatly increased background interference and so the error of the method became unduly large. However with improved shielding of the Geiger-Mueller tube and comparison of the counts to those obtained from a known source of radiation accurate measurement of the radio-iodide content of the thyroid could be made (13, 14, 15).

Recently the thyroid clearance of radio-iodide has been introduced as a more accurate measure of thyroid function for it deals with not only the percent of the dose of radio-iodide taken up by the thyroid in a given period but also the plasma concentration of radio-iodide that is presented to the gland over the same period (16).

Although it has been noted by various workers that in patients with cardiac and renal disease there is a delayed excretion of iodine (17, 18, 19, 20) which probably invalidates the use of excretion

studies as a means of assessing thyroid function little has been done to show whether decreased excretion of radio-iodide might invalidate the in vivo methods of assessing thyroid activity.

As many patients with kidney disease have low serum proteins assessment of thyroid activity by means of protein-bound iodine estimations must be interpreted cautiously as hypoproteinemia can lead to depressed protein-bound iodine levels approaching those found in myxoedema (21, 22). Also the basal metabolic rate, which even in normal subjects gives at best only an approximation of thyroid function, in these individuals is often low and probably more related to malnutrition than to decreased thyroid function and therefore not a reliable method for assessing thyroid activity. This problem is of more than academic interest for decreased renal function is relatively common clinically and so its chance association with thyroid dysfunction will occassionally occur. Selvaag noted the association of renal disease with thyrotoxicosis in 2% of all thyrotoxics (23).

The patient in congestive heart failure with tachycardia, auricular fibrillation, increased sweating and nervousness, and loss of flesh is a very frequent clinical problem in whom thyrotoxicosis must be ruled out as the etiologic factor. Basal metabolic rates in these patients are notoriously misleading for they are almost always high due to the patients dyspnoea. Protein-bound iodine values in these subjects are probably a more accurate means of assessing thyroid function but sometimes these patients have low

plasma proteins and most of them have a certain degree of hydraemia and therefore protein-bound iodine values might tend to be on the low side.

Therefore it seemed that a study of patients with cardiac and renal disease but no overt signs of thyroid dysfunction might show whether tracer techniques with radioactive iodine can be used as a reliable measure of thyroid activity in these individuals. Furthermore by taking into account such factors as the plasma level of stable iodide it appeared that information could be obtained as to whether or not renal and cardiac disease produced any change in thyroid function.

CHAPTER II

METHOD AND PROCEDURES FOLLOWED ON NORMAL SUBJECTS, PATIENTS WITH KIDNEY DISEASE AND PATIENTS IN CONGESTIVE HEART FAILURE

Patients with kidney disease were chosen as subjects only when they showed obvious signs of renal failure--elevated blood urea-nitrogen, gross albuminuria and poor urinary concentrating power. An attempt was made to study patients in congestive heart failure while their oedema was stationary. This was not possible in all cases as some were losing their oedema on digitalis and bed rest. None of the patients with renal disease or heart disease were on mercurial diuretics during or for at least 2 weeks prior to the study. All of the patients with congestive heart failure were on digitalis and salt-poor or salt-free diets. Eight of the 11 patients with kidney disease were on salt-poor diets. Details of these patients are to be seen in Tables I & II.

Normal controls were patients from the wards of the Winnipeg General Hospital suffering from conditions not known to affect either the kidneys or the thyroid gland. All patients were clinically euthyroid and this was checked in most cases by protein-bound plasma iodine estimations. These patients are listed in Table III.

Special care was taken to select subjects who had not

previously had organic iodine compounds (diodrast, priodax and lipiodal especially). None of the subjects had had any inorganic iodide medication for at least 2 months.

The mean age of patients with renal disease was 50.5 years; of patients with heart failure 69.4 years and for the control subjects 35.8 years.

The fasting patient after having voided was given 100 μc. of carrier-free radio-iodide orally. Approximately two hours later when the radio-iodide had been completely absorbed the subject emptied his bladder completely and a blood specimen was obtained and the time noted. Counts over the thyroid were begun shortly after this and midway, or as soon as 500 counts had been registered, a second blood sample was withdrawn and the time again noted. A measured clearance period of approximately 2 hours was allowed to elapse and the entire procedure was repeated; the subject remaining fasting all this time. By these procedures it was possible to determine renal and thyroid I-131 clearance rates. In addition to the clearance urine specimen 24 hour urine specimens were collected from most control and renal subjects until the asymptotic amount of radio-iodide had been excreted. It was found impossible to obtain accurate urine collections outside of the clearance period for patients in congestive heart failure. Another blood specimen was obtained 26 hours after the administration of the radio-iodide in most cases.

The quantity of radio-iodide present in the thyroid gland

was determined by the comparison of direct counts six inches above the thyroid isthmus using a shielded collimated Geiger tube (24, 25) with similar counts over a standard solution of radio-iodide in a glass container. At least 1000 counts were obtained in each instance. Background radiation was corrected for by subtracting a reading made six inches above the knee. Thyroid estimations were made at 2, 4, 26, 51, and 75 hours after the dose of radio-iodide was given.

Blood specimens were collected in heparin or balanced oxalate, centrifuged as soon as possible and the plasma decanted off. Protein-bound iodine estimations were made on the first plasma sample using the method of Barker (26) slightly modified (27). The plasma concentration of I-131 was estimated on each specimen as follows; Duplicate 1 ml. aliquots of plasma were taken and the proteins were precipitated with 3 ml. of 8% trichloracetic acid. The samples were centrifuged and 2 ml. of the supernatant were removed. One ml. of 1.5% potassium iodide was added to each and the iodine was precipitated with an excess of palladium chloride. The resulting palladium iodide was filtered onto a disc of filter paper, placed in a special holder and its radioactivity measured. The clearance urine specimens were treated similarly. A suitable aliquot of the dose of I-131 given was subjected to a similar precipitation and its radioactivity measured. Background radiation was subtracted from the total estimated radioactivity in each specimen. The results were expressed as a percentage of the given dose per 100 ml. of plasma or urine.

The initial 2 hour specimen and all urine passed following the clearance period was examined for radioactivity according to the following method. After measurement of the volume of the urine specimen duplicate 0.5 ml. aliquots were carefully pipetted by means of a micro-pipette into small dishes. To each dish was added one drop of 1.5% solution of KI and 0.2 ml. of $AgNO_3$ solution (containing 0.1 mgm. Ag per ml.). A standard was prepared by adding to one of the dishes an appropriate aliquot of the I-131 standard solution (usually 40 to 50 μc. in 500 ml. distilled water). The samples were evaporated to dryness without boiling under an infra red lamp and their radioactivity estimated. Background radiation was corrected for in both samples and the activity was expressed as a percentage of the administered dose. The cumulative excretion of radio-iodide was plotted against time and from inspection of the resultant curve the asymptotic amount was determined. From this figure and the excretion curve certain rates were calculated according to the method described by Keating et al. (28). These rates were the renal excretion rate (RER) and the extra renal disposal rate (ERDR).

Renal clearance of radio-iodide was computed using the conventional formula UV/P. However as the plasma level of the radio-iodide would fall in an exponentional manner in the period studied (29) a logarithmic mean concentration was calculated using the formula $\frac{P_1-P_2}{\text{Log}_e P_1-\text{Log}_e P_2}$ as suggested by Keating et al. (30). The clearance values were standardized to a body surface area of

1.73 square metres except for patients with congestive heart failure where because of oedema this was contraindicated. Endogenous creatinine clearance was estimated for the 2 hour clearance period and used as a measure of glomerular filtration rate. Endogenous creatinine clearance has been shown to follow inulin clearance fairly well in normals and patients with cardiac and renal disease (31). The creatinine clearance was also standardized to a body surface area of 1.73 square metres except in patients with congestive heart failure.

The percentage of radio-iodide reabsorbed by the kidney tubules was calculated in each case using endogenous creatinine clearance as the glomerular filtration rate and also by a formula derived by Platt (32) which, using only plasma and urinary concentrations of creatinine and I-131, offsets any error which may occur from the incomplete emptying of the bladder.

Thyroid plasma clearance rates for radio-iodide were obtained by dividing the percent of the dose accumulated by the thyroid per minute by the logarithmic mean plasma concentration of I-131 per ml. The thyroid accumulation rate of I-131 was computed from in vivo thyroid counts by the method of Keating et al. (30).

As the direct measure of inorganic iodide in plasma is technically difficult compared to its estimation in urine an indirect method of measuring it was used. This procedure is based on the assumption that the two isotopes, I-131 and I-127, chemically identical in the test tube, are metabolized in exactly the

same manner in the body. Since the kidneys excrete the isotopes indiscriminately there will be the same proportion of each in the plasma and in the urine. Or, expressed in another fashion, the ratio $\frac{\text{Urine I-127}}{\text{Urine I-131}} = \frac{\text{Plasma I-127}}{\text{Plasma I-131}}$. Therefore knowing three of the factors in the above equation, Plasma I-127 is readily calculated. Likewise by assuming that the thyroid is similarly non-selective the amount of I-127 picked up by the thyroid can be calculated from the following equation.

$$\frac{\text{Plasma I-127}}{\text{Plasma I-131}} = \frac{\text{I-127 picked up by thyroid per hour}}{\text{I-131 picked up by thyroid per hour}} .$$

The percent reabsorption of chloride and sodium loads by the kidney tubules were estimated on some subjects. Sodium was measured by internal standard flame photometry in serum and urine. Plasma chlorides were estimated according to the method of Schales and Schales (33), and urine chlorides by the method of Volhard-Arnold (34).

TABLE I

SHOWING CLINICAL DETAILS OF PATIENTS WITH RENAL DISEASE

Cases	Age	Sex	B.U.N. mgm.%	Plasma Creatinine mgm.%	Creatinine Clearance ml./min.°	P.B.I. µgm.%	Diet & Medication	Diagnosis
M.W.	50	M	38	1.1	52.6	7.8	S.P. & Insulin	Diabetes Mellitus & Kummel-stiel-Wilson's Disease
F.B.	56	M	34	1.3	56.5	4.7	S.P. & Dig.	Bilateral Pyonephrosis
H.A.	53	M	66	3.9	22.0	4.2	W.D.*	Chronic Nephritis
E.M.	25	M	23	2.0	48.8	4.0	S.P.*	Sub-acute Nephritis
M.R.	37	M	158	9.9	7.3	--	Intravenous	Polycystic Kidneys
B.S.	22	F	49	3.9	20.6	4.7	S.P. & Dig.	Chronic Nephritis & C.H.F.
A.H.	37	M	23	1.4	86.9	--	Insulin	Diabetes Mellitus & Kummel-stiel-Wilson's Disease
H.A.	75	M	48	2.1	24.4	4.2	W.D. & NaCl	Nephrosclerosis & mild C.H.F.
C.S.	52	M	21	1.1	87.0	3.3	S.P.	Chronic Nephritis
E.P.	74	M	34	1.4	37.5	4.9	S.P. & Insulin	Diabetes Mellitus & Kummel-stiel-Wilson's Disease
E.V.	74	M	31	1.6	30.4	3.7	S.P. & Dig.	Nephrosclerosis

* W.D. - Ward Diet
* S.P. - Salt-poor Diet
° - Standardized to body surface area of 1.73 sq. metres

TABLE II

SHOWING CLINICAL DETAILS OF PATIENTS WITH HEART FAILURE

Cases	Age	Sex	B.U.N. mgm.%	Plasma Creatinine mgm.%	Creatinine Clearance ml./min.°	P.B.I. µgm.%	Diet & Medication	Diagnosis
A.J.	83	M	18	1.0	52.3	—	S.P.* & Dig.	Arteriosclerotic Heart Disease
S.G.	59	M	28	0.9	59.1	3.7	S.P. & Dig.	Arteriosclerotic Heart Disease
W.M.	51	M	31	2.0	52.3	6.1	S.P. & Dig.	Rheumatic Heart Disease
T.H.	80	M	12	1.4	22.9	2.8	S.P. & Dig.	Arteriosclerotic Heart Disease
A.D.	75	M	29	3.8	15.5	2.7	S.P. & Dig.	Arteriosclerotic Heart Disease
W.G.	70	M	12	0.9	67.1	4.1	S.P. & Dig.	Arteriosclerotic Heart Disease
T.T.	68	M	--	1.2	53.5	3.6	S.P. & Dig.	Hypertensive Heart Disease

* S.P. - Salt-poor Diet
° - Not Standardized

TABLE III

SHOWING CLINICAL DETAILS OF NORMAL SUBJECTS

Cases	Age	Sex	B.U.N. mgm.%	Plasma Creatinine mgm.%	Creatinine Clearance ml./min.°	P.B.I. µgm.%	Diet & Medication	Diagnosis
J.J.	51	M	—	1.1	114	—	W.D.*	Spontaneous Pneumothorax
H.C.	43	M	—	0.7	108	—	W.D.	Fractured Femur
A.P.	71	M	—	1.1	83.3	—	W.D.	Fractured Humerus
M.N.	46	M	—	—	—	—	W.D.	Atopic Dermatitis
A.R.	25	M	—	0.8	114	5.0	W.D.	Normal
E.C.	32	M	16	1.0	95	5.0	W.D.	Normal
S.C.	37	M	12	1.1	107	4.2	W.D.	Methyl Hydrate Poisoning-- no kidney damage
C.N.	26	M	—	0.7	125	6.2	W.D.	Normal
W.P.	26	M	—	0.9	124	4.5	W.D.	Thumb Injury
J.H.	30	M	—	0.9	124	4.0	W.D.	Pneumonia
G.F.	21	M	—	0.9	146	4.2	W.D.	Convalescent Typhoid
D.S.	21	M	—	1.1	118	3.5	W.D.	Normal

* W.D. - Ward Diet
° - Standardized to body surface area of 1.73 sq. metres

TABLE IV

RENAL I-131 CLEARANCE

CONTROL SUBJECTS		PATIENTS WITH RENAL DISEASE		
Cases	ml./min.	Cases	ml./min.	
J.J.	22.3	M.W.	5.1	
H.C.	26.2	F.B.	5.0	
A.P.	30.7	H.A.	2.2	
M.N.	37.1	E.M.	3.4	
A.R.	26.7	M.R.	0.7	
E.C.	25.3	B.S.	7.4	$p<.01$
S.C.	25.4	A.H.	15.7	
C.N.	41.8	H.A.	6.7	
W.P.	35.6	C.S.	1.2	
J.H.	36.7	E.P.	7.5	
G.F.	42.7	E.V.	5.8	
D.S.	26.7			
Mean & S.E.	31.4 ±2.0	Mean & S.E.	5.5 ±1.2	

TABLE V

26 HOUR I-131 PLASMA CONCENTRATION

CONTROL SUBJECTS		PATIENTS WITH RENAL DISEASE		
Cases	% dose/100 ml. plasma	Cases	% dose/100 ml. plasma	
S.C.	.031	B.S.	.227	
C.N.	.023	A.H.	.364	
W.P.	.032	H.A.	.228	$p<.01$
J.H.	.029	C.S.	.106	
G.F.	.021	E.P.	.204	
D.S.	.024	E.V.	.128	
Mean & S.E.	.027 ±.0006	Mean & S.E.	.210 ±.012	

CHAPTER III

RESULTS PERTAINING TO SUBJECTS WITH RENAL LESIONS

The renal clearance of radio-iodide in 11 patients with kidney disease and in 12 control subjects is shown in Table IV. In the patients with kidney disease the rate at which plasma was cleared by the kidney of its radio-iodide averaged 5.5 ml. per min. with a standard error of 1.2. The renal radio-iodide clearance rate for the 12 controls averaged 31.5 ml. per min. with a standard error of 2.1. This difference was found to be statistically highly significant. This retention of I-131 is shown in Table V where the mean plasma level of I-131 26 hours after the administration of the dose in 6 control subjects was .027 percent of the dose per 100 ml. compared to .210 percent of the dose per 100 ml. in 6 patients with renal disease.

The explanation for the defective clearance of I-131 by patients with renal disease is shown by the results in Tables I & IV. It will be noted that not only was the filtration rate decreased in these individuals but also the mean tubular reabsorption of filtered I-131 was increased (Table VI). This retention of I-131 was further exemplified by the urine excretion curves which were found to be flattened and prolonged in patients with renal disease as compared to the control subjects. A curve from a typical patient with renal disease and a typical normal curve are shown in Figure I.

The 48 hour excretion of I-131 was also found to be considerably less for patients with renal dysfunction as compared to the control individuals (Table VIII). This difference is statistically highly significant.

The R.E.R. (Keating) of I-131 was similarly found to be significantly less for patients with kidney disease as compared to normal subjects (Table VIII).

In Table VIII it is seen that the E.R.D.R. for patients with renal disease was significantly less than that noted for the control group. It was noted that the percent reabsorption of sodium and chloride by the kidney tubules of patients with renal disease was somewhat less than in the control subjects (Table VII).

Most of the control subjects had picked up their maximum amount of radio-iodide in the thyroid gland by 26 hours after the administration of the dose. In a few this was increased in the following 24 hours, but this never amounted to more than 1.4% of the dose (Figure IIA). The results obtained in 10 patients with renal dysfunction were markedly different. It will be seen in Figure IIB that while at 26 hours the values were similar to those of the control group this level was reached more slowly and was in all cases followed by a further rise. Two cases, E.M. and E.V., with chronic nephritis and nephrosclerosis respectively showed rather remarkable curves for I-131 thyroid uptake with a maximum pick-up at 75 hours of 60% and 47% of the dose. These patients were clinically euthyroid and the protein-bound iodide levels were

TABLE VI

REABSORPTION OF FILTERED I-131

CONTROL SUBJECTS		PATIENTS WITH RENAL DISEASE		
Cases	Percent	Cases	Percent	
J.J.	80.5	M.W.	90.4	
H.C.	75.7	F.B.	91.2	
A.P.	63.2	H.A.	90.4	
A.R.	76.7	E.M.	93.0	
E.C.	73.4	M.R.	99.0	
S.C.	76.2	B.S.	66.4	
C.N.	66.5	A.H.	81.9	$p < .01$
W.P.	71.5	H.A.	72.7	
J.H.	70.6	C.S.	98.6	
G.F.	70.7	E.P.	80.0	
D.S.	77.4	E.V.	80.9	
Mean & S.E.	72.9 ±1.5	Mean & S.E.	85.9 ± 3.1	

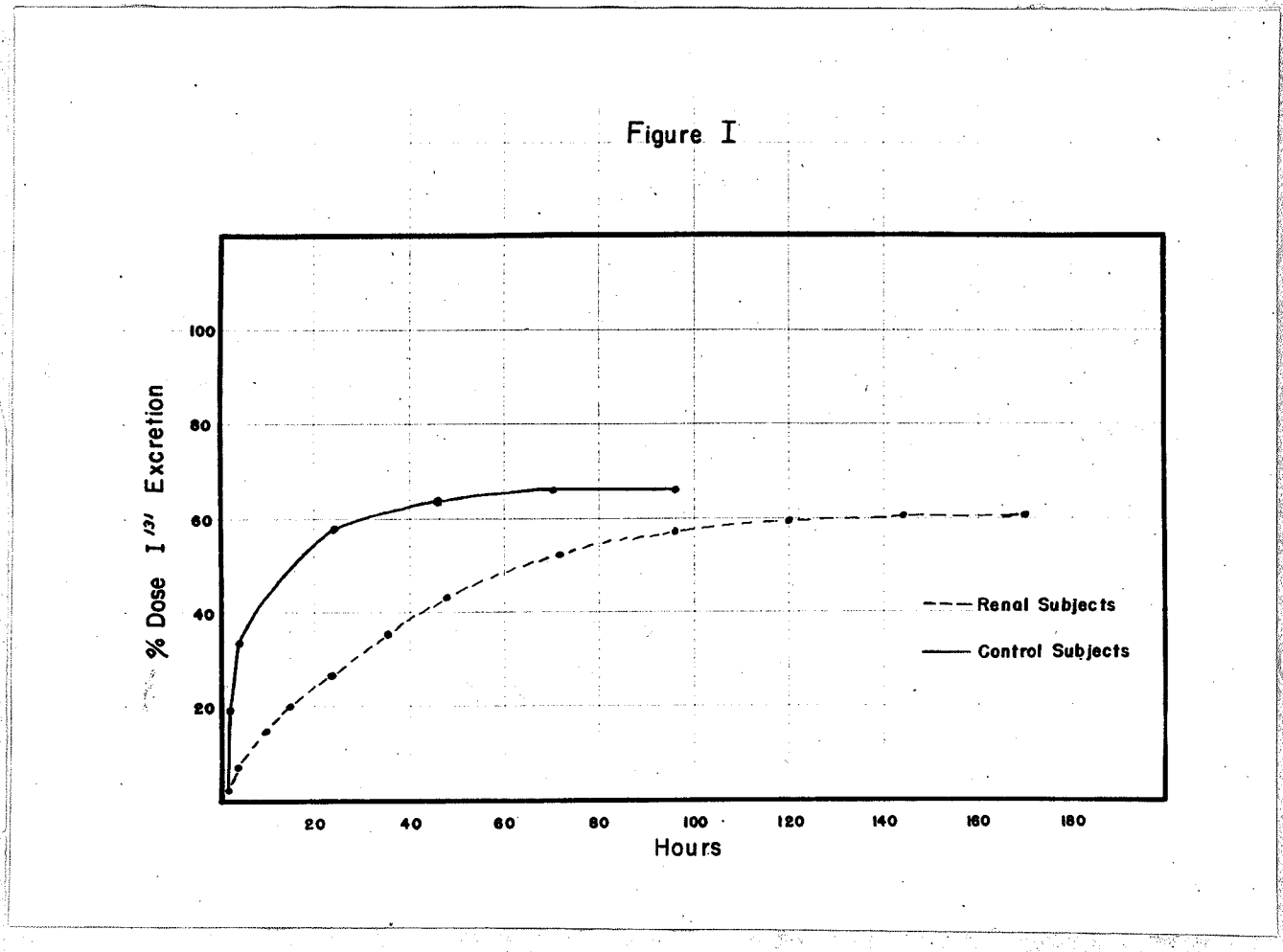
TABLE VII

REABSORPTION OF CHLORIDE AND SODIUM

CONTROL SUBJECTS			PATIENTS WITH RENAL DISEASE		
Cases	Chloride %	Sodium %	Cases	Chloride %	Sodium %
A.R.	99.1	99.8	E.P.	98.2	98.8
G.F.	98.4	99.1	E.V.	98.2	98.7
D.S.	99.5	99.7			

FIGURE I

TYPICAL URINARY EXCRETION CURVES OF I-131 FOR CONTROL SUBJECTS AND FOR PATIENTS WITH RENAL DISEASE



within normal limits (Table I).

Corresponding to the flattened thyroid uptake curve previously noted for patients with renal disease it will be seen that the mean thyroid clearance rate in these patients is considerably less than that noted for the control group (Table IX). This difference is statistically highly significant.

The mean A.R. (Keating) at 4 hours for 10 patients with kidney disease was 1.8 with a standard error of 0.2. In 12 control individuals the mean A.R. was 4.2 with a standard error of 0.6. This difference is highly significant (Table X).

The mean fasting plasma I-127 concentration in 7 control individuals was 0.17 µgm. per 100 ml. In 6 patients with renal disease the mean plasma iodide concentration was 2.2 µgm. per 100 ml. (Table XI).

The mean rate of I-127 thyroid uptake in 7 control subjects was 1.08 µgm. per hour. In 6 persons with diminished renal function, the mean rate was 2.9 µgm. per hour (Table XI).

TABLE VIII

URINARY EXCRETION OF I-131

CONTROL SUBJECTS				PATIENTS WITH RENAL DISEASE				
Cases	48 hr. excretion % dose	R.E.R. %/hr.	E.R.D.R. %/hr.	Cases	48 hr. excretion % dose	R.E.R. %/hr.	E.R.D.R. %/hr.	
H.C.	72.3	9.1	3.1	M.W.	49.4	1.8	1.1	
A.P.	65.3	6.4	2.0	H.A.	59.0	1.9	0.5	
M.N.	85.0	7.1	1.9	E.M.	24.0	0.7	1.5	48 hr. urinary excretion
A.R.	95.0	13.2	3.9	M.R.	2.4	--	--	$p < .01$
E.C.	85.0	12.1	2.9	B.S.	44.7	1.7	0.7	R.E.R.
S.C.	86.9	--	--	A.H.	78.0	--	--	$p < .01$
C.N.	66.1	14.9	9.4	H.A.	50.5	1.8	0.6	E.R.D.R. $p < .01$
W.P.	89.0	11.4	1.6	C.S.	46.0	2.0	0.5	
J.H.	64.0	10.1	4.9	E.V.	21.0	1.2	2.8	
G.F.	74.0	7.6	2.6					
Mean & S.E.	78.3 ±3.5	10.2 ±1.0	3.6 ±.8	Mean & S.E.	41.7 ±7.5	1.6 ±.3	1.1 ±.3	

FIGURE II A and FIGURE II B

I-131 THYROID UPTAKE CURVES FOR PATIENTS WITH RENAL DISEASE and FOR NORMAL SUBJECTS

Figure II A

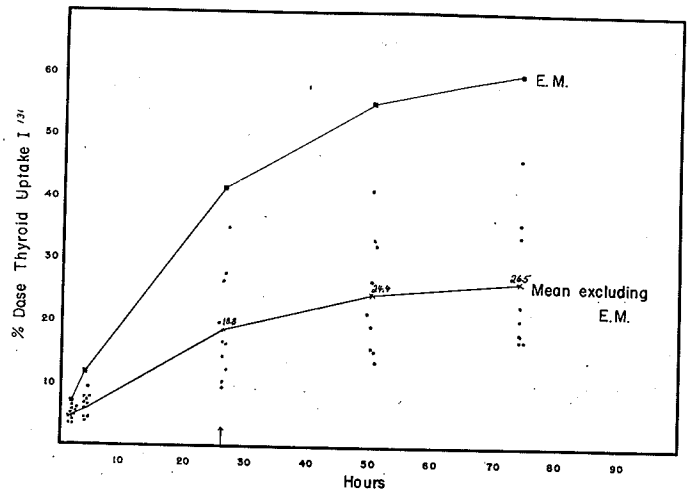


Figure II B

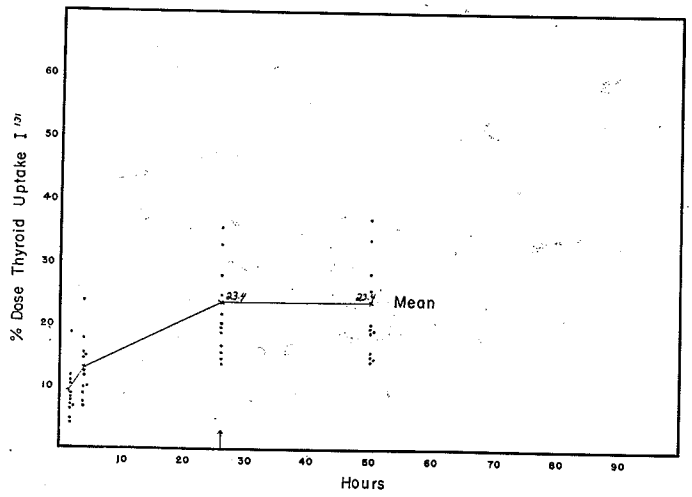


TABLE IX

THYROID CLEARANCE OF I-131

CONTROL SUBJECTS		PATIENTS WITH RENAL DISEASE		
Cases	ml./min.	Cases	ml./min.	
J.J.	35.8	M.W.	1.6	
H.C.	8.4	F.B.	5.3	
A.P.	6.0	H.A.	1.0	
M.N.	11.5	E.M.	18.0	
A.R.	7.6	M.R.	3.1	
E.C.	3.3	B.S.	3.7	$p < .02$
S.C.	15.1	A.H.	0.9	
C.N.	19.2	H.A.	3.1	
W.P.	4.2	C.S.	2.0	
J.H.	13.6	E.V.	8.6	
G.F.	12.0	E.P.	0.02	
D.S.	8.7			
Mean & S.E.	12.1 ± 2.5	Mean & S.E.	4.3 ± 1.5	

TABLE X

ACCUMULATION RATE (KEATING)

CONTROL SUBJECTS		PATIENTS WITH RENAL DISEASE		
Cases	Percent/hr.	Cases	Percent/hr.	
J.J.	5.6	M.W.	1.0	
H.C.	3.7	F.B.	2.1	
A.P.	1.9	H.A.	2.1	
M.N.	2.5	E.M.	3.0	
A.R.	3.7	M.R.	1.7	
E.C.	3.1	B.S.	1.7	
S.C.	5.3	A.H.	1.1	$p < .01$
C.N.	9.5	H.A.	1.7	
W.P.	2.7	C.S.	1.7	
J.H.	4.7	E.V.	2.2	
G.F.	2.9			
D.S.	4.6			
Mean & S.E.	4.2 $\pm$.6	Mean & S.E.	1.8 $\pm$.2	

TABLE XI

FASTING PLASMA I-127 CONCENTRATION
and
THYROID I-127 UPTAKE RATE

CONTROL SUBJECTS			PATIENTS WITH RENAL DISEASE		
Cases	I-127 conc. µgm./100 ml.	I-127 uptake µgm./hr.	Cases	I-127 conc. µgm./100 ml.	I-127 uptake µgm./hr.
A.R.	0.06	0.28	B.S.	2.70	5.60
S.C.	0.15	1.40	A.H.	2.40	1.30
C.N.	0.09	1.00	H.A.	1.40	2.70
W.P.	0.26	0.64	C.S.	3.80	4.50
J.H.	0.01	0.89	E.P.	2.20	0.23
G.F.	0.38	2.25	E.V.	0.54	2.80
D.S.	0.21	1.07			
Mean & S.E.	0.17 ±.005	1.08 ±.23	Mean & S.E.	2.20 ±.5	2.90 ±.8

I-127 Concentration $p < .01$

I-127 Uptake $p < .05$

TABLE XII

THE AMOUNT OF I-131 FILTERED DURING THE CLEARANCE PERIOD

CONTROL SUBJECTS		PATIENTS WITH RENAL DISEASE	
Cases	I-131 filtered % dose	Cases	I-131 filtered % dose
A.P.	.2750	M.W.	.2178
H.C.	.3582	F.B.	.1715
J.J.	.2178	H.A.	.3016
E.C.	.6688	E.M.	.1216
A.R.	.5267	M.R.	.0255
S.C.	.4697	B.S.	.1171
C.N.	.3050	A.H.	.6281
W.P.	.5810	H.A.	.1082
J.H.	.3323	C.S.	.2902
G.F.	.3103	E.P.	.1489
D.S.	.3965	E.V.	.0886
Mean & S.E.	.4037 ±.0424	Mean & S.E.	.2017 ±.0495

$p < .01$

CHAPTER IV

DISCUSSION OF RESULTS ON SUBJECTS WITH RENAL LESIONS

In any investigation in which urinary clearance studies are used there is always considerable doubt as to whether the bladder is completely emptied before and after each clearance period. Evidence that the bladder was completely emptied in all but one of the cases is shown by the close agreement of percentage tubular reabsorption as computed by ordinary methods with that of Platt (32) which offsets errors in urine collection by measuring only concentrations (Table XX).

In the 11 patients with renal disease investigated it was quite evident clinically that there was considerable damage to the kidney parenchyma (Table I). All of the patients had elevated values for blood urea-nitrogen; showed persistent albuminuria and low fixed urinary specific gravities. All of the patients had elevated plasma creatinine levels. Therefore it is probably not surprising that these same patients were found to have markedly decreased renal clearance rates for radio-iodide and to show considerable elevation of the 26 hour I-131 plasma concentration (Tables IV & V).

It has been shown by Riggs that iodide clearance rates in normal dogs can be greatly decreased by a low sodium chloride

intake (35). Eight of the patients with kidney disease were on low salt intake; but two on normal diets and one on a normal diet plus 2 grams of extra sodium chloride per day showed a mean radio-iodide clearance rate of 4.6 ml. per min. which is somewhat below that of the group as a whole. Therefore, although low salt intake may depress kidney radio-iodide clearance, the main cause of the decreased clearance rate in patients with renal disease is probably glomerular and tubular pathology.

The glomerular filtration rate, as measured by endogenous creatinine clearance, was found to be considerably decreased in the 11 patients with kidney disease (Table I). This resulted in most cases in a decrease in the amount of radio-iodide that was filtered during the clearance period; the mean value for 11 renal cases being .2017 ± .0495 (S.E.) % of the dose per minute as compared to .4037 ± .0424 (S.E.) % of the dose per minute for the 10 control individuals (Table XII). Therefore considerable retention of radio-iodide resulted from the glomerular damage in these patients. One case however with a relatively high blood level of radio-iodide filtered .628% of the dose per minute. The retention of radio-iodide was not due entirely to poor filtration for it is seen that the tubular reabsorption of radio-iodide was increased in patients with renal disease as shown in Table VI.

It is interesting that in cases B.S. and H.A., who had severe renal disease but who also were in heart failure at the time of this study showed a lower than normal percentage reabsorption

of I-131 (Table VI). Platt noted a similar change in tubular action in patients with renal disease who reabsorbed less of the sodium load than normal but that once congestive heart failure was superadded tended to retain sodium by increasing tubular reabsorption (32).

In summary then, in patients with kidney disease there is retention of a given dose of radio-iodide. This occurs because of decreased filtration and increased tubular reabsorption. It is possible that the low salt intake of some of these patients tended to depress, still further, the glomerular filtration rate (36) and increase the tubular reabsorption of radio-iodide (35).

A dissimilarity of tubular function in respect to sodium and chloride on the one hand and iodide on the other has appeared in the present study. The percentage reabsorption of iodide by the kidney tubules in normal individuals has been estimated at 73% by Homer Smith (37). The results in this series using physiological amounts of iodide as the radioactive isotope agree well with this figure (Table VI). However the percentage of the sodium load reabsorbed by normally functioning kidney tubules is in the region 98-99% (Table VII). Probably more remarkable is the fact that chloride, which is so similar to iodide chemically, is reabsorbed by the kidney tubules in percentage amounts almost identical to those noted for sodium (Table VII). It has been shown recently by Platt that although patients with renal failure filter less sodium than normal they reabsorb a smaller percentage of the tubu-

lar load (32). This has been confirmed in 2 of the patients with renal disease who even though they were on salt-poor diets and fasting still reabsorbed only 98.8 and 98.7% of the sodium load (Table VII).

It is interesting that in patients with renal failure there is an increase in the percent tubular reabsorption of iodide but a fall in the percent reabsorption of sodium and probably chloride.

Platt found that the reduction of tubular reabsorption of sodium noted in patients with kidney failure tended to increase as the glomerular filtration rate decreased so as to maintain normal plasma levels of sodium (32). In the present series there was no correlation between filtration rate and the degree of iodide reabsorption.

It has been noted by various workers that there is a delay in the excretion of a given dose of I-131 in patients with impaired renal function (18, 38). In all of our patients with renal disease there was indeed a considerable delay in the excretion of a test dose of I-131. It is important to know whether this delayed excretion is sufficiently great to invalidate excretion studies of I-131 as a means of assessing thyroid function in such individuals.

The 48 hour urinary excretion of I-131 expressed as a percent of the given dose is a popular method of testing thyroid function. The accepted range for euthyroid individuals is given as 45-82% (18). In this series of 9 patients with renal disease the 48 hour urinary excretion of I-131 averaged 41.7 with a stan-

dard error of 7.5 (Table VIII). These values place almost half of these individuals in the thyrotoxic range. Clinically however these patients were euthyroid and their protein-bound iodine estimations were within normal limits (Table I). Therefore it is obvious that in patients with significantly depressed renal function the 48 hour urinary excretion of I-131 gives misleading results.

Keating has advanced an index, the extra renal disposal rate (ERDR) of I-131, as being a good test of thyroid function (28). This is derived from the urinary excretion curve of I-131 following the administration of a test dose. Therefore it is probably not remarkable that in the 7 patients with renal disease this value was outside the accepted normal range. As is shown in Table VIII the E.R.D.R. for 7 patients with renal dysfunction was 1.1± 0.3 (S.E.); the accepted range for euthyroid subjects being 1.3-7.9 (18). Whether this value is abnormally low because in renal disease the assumptions on which the formula is based are at fault, or whether it is a reflection of the decreased thyroid accumulation and clearance rates also noted in these individuals (Tables IX & X) is not at all clear. However it is seen from Tables VIII & X that in every case but one the E.R.D.R. is considerably less than the A.R. calculated from in vivo thyroid measurements while they agree fairly well in the control subjects. It seems therefore that the abnormally low E.R.D.R. is not solely due to decreased thyroid accumulation rate but is a reflection of diminished renal function. In any case this factor does not give a true value for thyroid

function as these patients were clinically euthyroid and had normal protein-bound iodine values.

As is shown in Figure IIA the thyroids of patients with kidney disease continued to take up radio-iodide after the 26 hour period in marked contrast to the normal controls, who, for the most part had picked up their maximum amount of radio-iodide by this time (Figure IIB). Due to the retention of radio-iodide by these individuals, as shown by decreased renal clearance rates and by high plasma I-131 concentration at 26 hours (Tables IV & V), the thyroids are presented with higher plasma levels of radio-iodide for longer periods of time and so might be expected to continue to take up radio-iodide.

In the 11 patients with renal dysfunction there was a significant decrease in the thyroid radio-iodide clearance rate and in the A.R. (Keating) (Tables IX & X). Essentially this means that the thyroid glands of these individuals were taking up a smaller percentage of the given dose of radio-iodide per unit time. This can be due to two factors; that the thyroid avidity for iodine is decreased or that this depression in clearance rate is due to dilution of the isotope with high blood levels of stable iodide.

In the 6 patients with renal disease on whom plasma I-127 was calculated the mean concentration was 2.2 µgm. per 100 ml., which was considerably higher than that found for 7 control subjects (Table XI). There was therefore considerable dilution of I-131 by stable iodide in the plasma of patients with kidney dys-

function and as the thyroid picks up only a portion of the iodide presented to it a decrease in the rate of I-131 uptake might be expected. To determine if the depression of I-131 uptake by the thyroid in these cases was due to a dilution factor the actual amount of I-127 entering the thyroid per hour was calculated. Table XI shows that in 6 patients with renal disease, on whom calculations were made, the amount of I-127 that was entering the thyroid gland per hour was actually higher than in the control subjects. This increase in stable iodide uptake with high plasma levels has been noted by Stanley ih acute experiments (39). In an attempt to explain the higher values obtained for I-127 uptake it should be noted that the protein-bound iodine estimations on these patients were normal and there was no clinical evidence of increased peripheral utilization of hormone. Thus the increased uptake of stable iodide does not appear to be due to an increase in hormone formation. The simplest explanation of this phenomenon is that due to the high levels of circulating iodide and presumably of inorganic iodide of the thyroid which is in equilibrium with it, the interchange of iodine molecules proceeds at a faster rate following Le Chatelier's principle, but that hormone formation goes on at a rate governed only by the level of thyroid stimulating hormone and unaffected by the higher blood and thyroid inorganic iodide concentrations.

It is concluded that the low thyroid I-131 clearance rates and A.R. found in patients with poorly functioning kidneys does

not indicate a disturbance of hormone formation and is due to the dilution of the radioactive isotope by high blood levels of stable iodide.

Despite the marked lowering of the I-131 thyroid plasma clearance rate in patients with renal disease it was noted that the 26 hour uptake of I-131, as measured by in vivo counts over the thyroid gland, was only slightly lower than that noted for normal individuals (Figures IIA & IIB). This is explained by the fact that there are two opposites working in this case: one, the dilution factor tending to lower the amount of I-131 that enters the gland and two, the retention factor which, by decreasing the natural fall of I-131 concentration in the blood over the 26 hour period, tends to increase the amount of I-131 that enters the gland in this period. In 11 patients the 26 hour uptake was within normal limits, albeit on the low side, except in one elderly man. It has been noted by various workers that elderly people have thyroid uptakes in the low range of normal (40). It seems therefore that the 26 hour in vivo uptake of I-131 in patients with renal disease gives a figure which, although slightly low, is the best indication of true thyroid function in these individuals.

SUMMARY

In the cases of kidney disease studied there was retention of a given dose of radio-iodide. This was demonstrated by a diminished renal clearance rate for radio-iodide, diminished R.E.R. and 48 hour excretion, and by an increase in the 26 hour plasma level of the isotope. This retention of radio-iodide was brought about not only by a decrease in the amount filtered, but also by an increase in the percentage of filtered radio-iodide reabsorbed by the kidney tubules. Possibly the low salt diet of some of these patients contributed to the retention of radio-iodide by decreasing the glomerular filtration rate and increasing the amount of radio-iodide reabsorbed by the tubules.

Percent iodide reabsorption by the normal kidney tubules was less than that for sodium and chloride but approaches it in renal failure. Percent iodide reabsorption by the kidney tubules increases in renal failure, whereas sodium and probably chloride reabsorption decreases with kidney failure.

Radio-iodide continued to be taken up by the thyroid glands of patients with renal disease for periods of three days or more. This was in marked contrast to the control group, the majority of whom ceased to increase their thyroid radio-iodide after 26 hours.

The thyroid clearance rate of I-131 and A.R. was significantly decreased in patients with kidney disease. However, the thyroids of these same patients, although clearing less plasma

of I-131, were shown to be exchanging stable iodine with the plasma at a faster rate than the control group. Thus thyroid clearance rates of I-131, as a measure of thyroid function in patients with renal disease, give a false impression of decreased thyroid activity. The 26 hour thyroid in vivo count was concluded to give a figure which although somewhat low is probably the best indication of thyroid function in patients with renal failure.

TABLE XIII

RENAL I-131 CLEARANCE

CONTROL SUBJECTS Cases	ml./min.	PATIENTS IN HEART FAILURE Cases	ml./min.	
M.N.	37.1	A.J.	19.4	
A.P.	30.7	S.G.	27.3	
H.C.	26.2	W.M.	22.2	
J.J.	25.6	T.H.	6.6	
E.C.	25.6	A.D.	6.1	
A.R.	32.9	W.G.	20.1	$p<.01$
S.C.	24.2	T.T.	12.6	
C.N.	47.9			
W.P.	37.0			
J.H.	40.0			
G.F.	44.4			
D.S.	29.2			
Mean & S.E.	33.4 ±2.3	Mean & S.E.	16.3 ±3.0	

TABLE XIV

26 HOUR I-131 PLASMA CONCENTRATION

CONTROL SUBJECTS Cases	% dose/100 ml. plasma	PATIENTS IN HEART FAILURE Cases	% dose/100 ml. plasma	
S.C.	.031	A.J.	.063	
C.N.	.023	S.G.	.061	
W.P.	.032	W.M.	.052	
J.H.	.029	T.H.	.086	$p<.01$
G.F.	.021	A.D.	.146	
D.S.	.024	W.G.	.113	
		T.T.	.051	
Mean & S.E.	.027 ±.0006	Mean & S.E.	.082 ±.014	

CHAPTER V

RESULTS PERTAINING TO PATIENTS IN CONGESTIVE HEART FAILURE

It was found impossible to obtain accurate urine collections outside the clearance period because of the illness of the patients concerned. These patients however were excreting a tracer dose of I-131 more slowly than the control subjects as is shown by the decreased clearance of I-131 and the increased mean plasma I-131 level at 26 hours (Tables XIII & XIV).

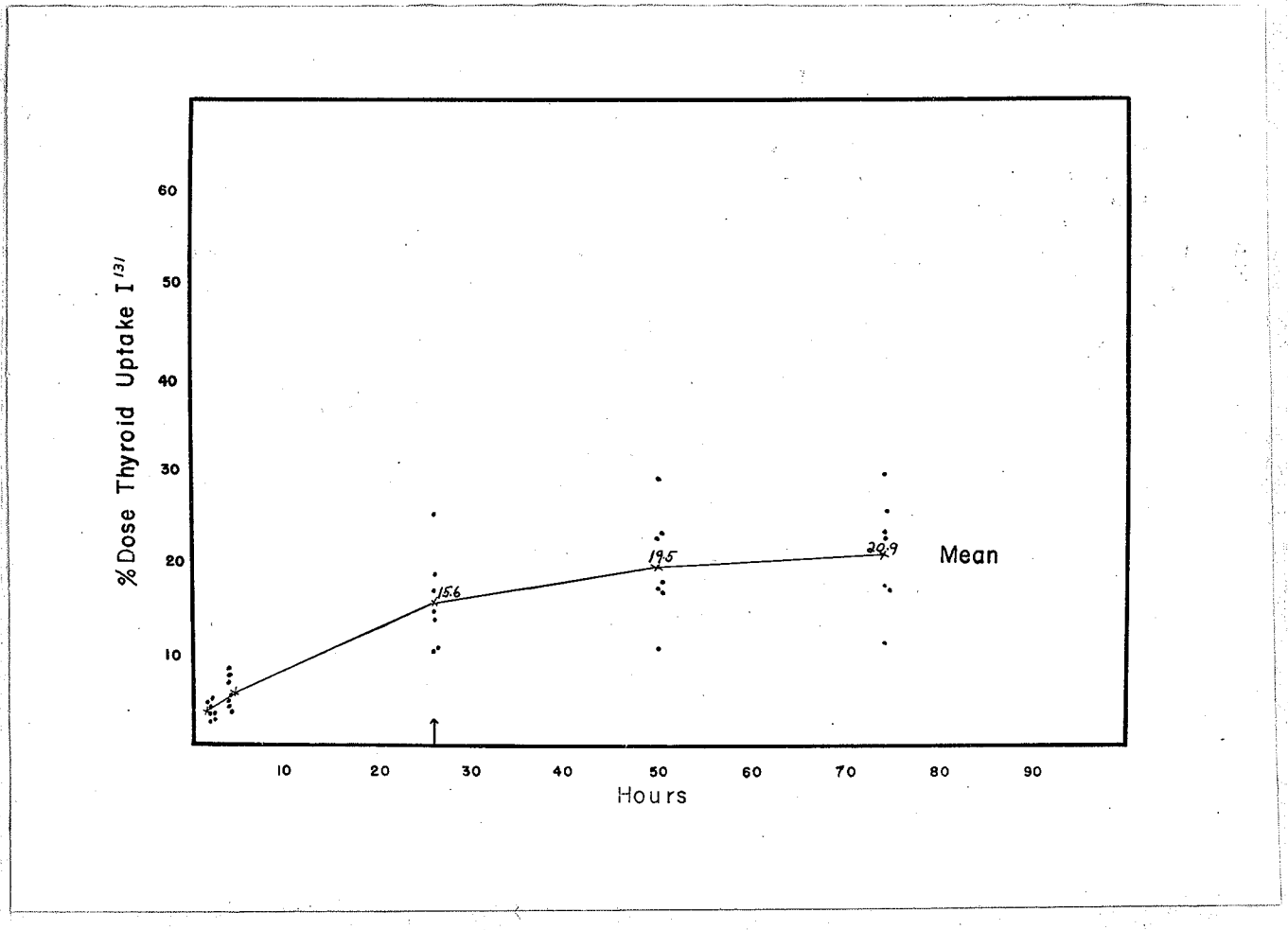
In contrast to the overall retention of I-131 noted for the patients with congestive heart failure it is shown in Table XV that the percent of the I-131 load reabsorbed by the kidney tubules was significantly less than for the control individuals.

As has been noted in renal disease, the tubular reabsorption of sodium for patients with congestive heart failure digressed from the control value in a direction opposite to that for iodide (Tables XIX & XV).

The accumulation of I-131 by the thyroid glands of patients with heart disease proceeded at a slower rate than the control group. It was noted however that while in the control group the thyroid accumulation curve had flattened at 26 hours, in patients with congestive heart failure there was a steady rise up to 74 hours in most cases (Figure IV).

FIGURE IV

I-131 THYROID UPTAKE CURVES FOR PATIENTS WITH HEART FAILURE



Corresponding to the flattened thyroid uptake curve previously noted for patients with congestive heart failure it is seen that the mean thyroid plasma clearance and the thyroid A.R. (Keating) are both less than that noted for the control group (Table XVI). This decrease however is in no way as marked as that noted for patients with renal failure (Tables IX & X).

The mean fasting plasma I-127 concentration in the 6 patients with congestive heart failure was 0.24 µgm. per 100 ml. as compared to 0.17 µgm. per 100 ml. for 7 control subjects (Table XVII).

The mean rate of I-127 exchange by the thyroid was 1.08 µgm. per hour for the 7 control individuals as compared to 0.70 µgm. per hour for 6 patients with congestive heart failure.

TABLE XV

REABSORPTION OF FILTERED I-131

CONTROL SUBJECTS		PATIENTS IN HEART FAILURE		
Cases	Percent	Cases	Percent	
J.J.	80.5	A.J.	63.0	
H.C.	75.7	S.G.	53.9	
A.P.	63.2	W.M.	57.5	
A.R.	76.7	T.H.	71.0	
E.C.	73.4	A.D.	60.4	
S.C.	76.2	W.G.	70.0	$p < .05$
C.N.	66.5	T.T.	76.3	
W.P.	71.5			
J.H.	70.6			
G.F.	70.7			
D.S.	77.4			
Mean & S.E.	72.9 ± 1.5	Mean & S.E.	64.6 ± 3.1	

TABLE XVI

THYROID CLEARANCE OF I-131
and
ACCUMULATION RATE (KEATING)

CONTROL SUBJECTS			PATIENTS IN HEART FAILURE		
Cases	T.C. ml./min.	A.R. %/hr.	Cases	T.C. ml./min.	A.R. %/hr.
J.J.	35.8	5.6	A.J.	4.0	1.2
H.C.	8.4	3.7	S.G.	7.7	2.0
A.P.	6.0	1.9	W.M.	8.1	2.3
M.N.	11.5	2.5	T.H.	3.4	1.0
A.R.	7.6	3.7	A.D.	2.9	0.8
E.C.	3.3	3.1	W.G.	4.7	1.3
S.C.	15.1	5.3	T.T.	10.0	2.1
C.N.	19.2	9.5			
W.P.	4.2	2.7			
J.H.	13.6	4.7			
G.F.	12.0	2.9			
D.S.	8.7	4.6			
Mean & S.E.	12.1 ±2.5	4.2 ±.6	Mean & S.E.	5.8 ±1.0	1.5 ±.2

T.C. $p < .05$

A.R. $p < .01$

TABLE XVII

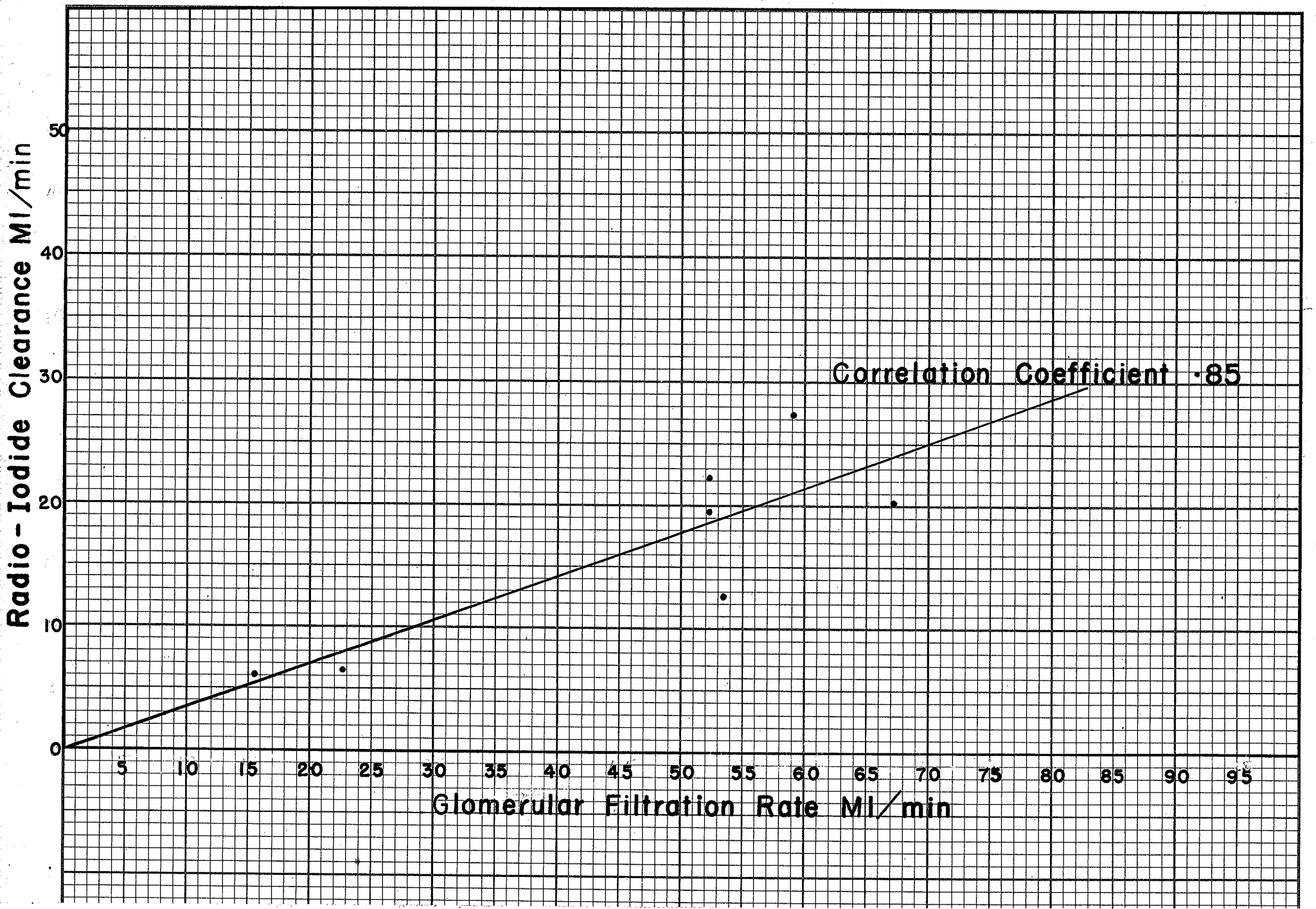
FASTING PLASMA I-127 CONCENTRATION
and
THYROID I-127 UPTAKE RATE

CONTROL SUBJECTS			PATIENTS IN HEART FAILURE		
Cases	I-127 conc. µgm./100 ml.	I-127 uptake µgm./hr.	Cases	I-127 conc. µgm./100 ml.	I-127 uptake µgm./hr.
A.R.	0.06	0.28	A.J.	.22	.52
S.C.	0.15	0.40	S.G.	.27	1.24
C.N.	0.09	1.00	T.H.	.45	.91
W.P.	0.26	0.64	A.D.	.12	.25
J.H.	0.01	0.89	W.G.	.18	.05
G.F.	0.38	2.25	T.T.	.21	1.26
D.S.	0.21	1.07			
Mean & S.E.	0.17 ±.005	1.08 ±.23	Mean & S.E.	.24 ±.005	.70 ±.18

I-127 Concentration $p > .3$

I-127 Uptake $p > .2$

Figure III


Radio-Iodide Clearance Ml/min
50
40
30
20
10
0
Correlation Coefficient ·85
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95
Glomerular Filtration Rate Ml/min

CHAPTER VI

DISCUSSION OF RESULTS PERTAINING TO PATIENTS IN CONGESTIVE HEART FAILURE

The collection of urine over the clearance period was an accurate measure of kidney output as shown by the close agreement of figures obtained for the percentage tubular reabsorption by the conventional method and by the method described by Platt (32), which as stated above deals only with concentrations and therefore rules out errors of urine collection (Table XX).

The decreased renal clearance of I-131 noted for the 7 patients with congestive heart failure (Table XIII) correlated fairly well with their respective endogenous creatinine clearance rates (R=.85) (Figure III). As the percent reabsorption of the iodide load to the tubules is on the average less than normal (Table XV) it would appear that the decreased excretion of I-131 in congestive heart failure is due largely to decreased filtration.

It has been shown that in normal dogs on low sodium chloride intake and hence conserving salt tubular reabsorption of iodide is almost complete (35). It is interesting to note that patients with congestive heart failure who are involuntarily conserving salt have decreased rather than increased tubular reabsorption of iodide.

There is a slower excretion of the administered tracer

TABLE XVIII

I-131 CONCENTRATION AT 4 HOURS

CONTROL SUBJECTS		PATIENTS IN HEART FAILURE		
Cases	% dose	Cases	% dose	
G.F.	.157	W.G.	.274	
J.H.	.196	A.D.	.205	
W.P.	.384	T.H.	.220	
C.N.	.188	W.M.	.260	
S.C.	.344	S.G.	.288	
A.R.	.386	A.J.	.318	
E.C.	.643	T.T.	.232	p>.5
J.J.	.145			
H.C.	.250			
A.P.	.275			
M.N.	.155			
D.S.	.285			
Mean & S.E.	.284 ±.041	Mean & S.E.	.257 ±.015	

TABLE XIX

REABSORPTION OF FILTERED CHLORIDE AND SODIUM

CONTROL SUBJECTS			PATIENTS IN HEART FAILURE		
Cases	Chloride %	Sodium %	Cases	Chloride %	Sodium %
A.R.	99.1	99.8	T.H.	99.7	99.9
G.F.	98.4	99.1	A.D.	99.0	99.2
D.S.	99.5	99.7	W.G.	99.2	99.5
			T.T.	99.6	99.7

dose of I-131 in patients in congestive heart failure than in the control subjects. The degree of this retention of a given dose of I-131 is shown by a decreased renal clearance rate and by an elevation of the 26 hour plasma concentration of I-131 (Tables XIII & XIV). As might be expected this retention of I-131 resulted in a steady increment in the thyroid uptake past the usual asymptote at 26 hours and in most cases the thyroid uptake did not reach its maximum level until 74 hours after the administration of the dose (Figure IV).

The thyroid plasma clearance rates and A.R. (Keating) for the patients in congestive heart failure were lower than those of the control subjects (Table XVI). These cardiac patients were clinically euthyroid and this was confirmed in all but 2 cases by normal protein-bound iodine estimations (Table II). Two patients, T.H. and A.D. had protein-bound iodine levels that were below normal. Both of these patients had low plasma albumin concentrations (3.5 mgm. per 100 ml. and 3.2 mgm. per 100 ml.) which would tend to lower protein-bound iodine levels (22). It is possible that hydraemia might play a part in the concentration of protein-bound iodine in the plasma as both these patients were markedly oedematous. Thus if we consider that these patients are clinically and biochemically euthyroid the decrease in the thyroid plasma clearance could only be explained on a dilution of the tracer dose by high blood levels of I-127 or that the tracer dose is distributed through the large volume of oedema fluid. It is possible that a

TABLE XX

SHOWING AGREEMENT BETWEEN TWO METHODS OF CALCULATING % REABSORPTION

CONTROL SUBJECTS			PATIENTS WITH RENAL DISEASE			PATIENTS IN HEART FAILURE		
Cases	Platt	Conventional	Cases	Platt	Conventional	Cases	Platt	Conventional
A.P.	63.2	63.1	M.W.	90.4	90.6	A.J.	63.0	63.1
H.C.	75.7	75.6	F.B.	91.2	91.1	S.G.	53.9	53.8
J.J.	80.5	80.7	H.A.	90.4	90.7	W.M.	57.5	57.6
E.C.	73.4	73.5	E.M.	93.0	93.2	T.H.	71.0	70.9
A.R.	76.7	76.5	M.R.	99.0	90.6	A.D.	60.5	60.4
S.C.	76.2	76.3	B.S.	66.4	67.4	W.G.	70.0	70.0
C.N.	66.5	66.7	A.H.	81.9	82.0	T.T.	76.3	76.3
W.P.	71.5	71.3	H.A.	72.7	72.4			
J.H.	70.6	70.7	C.S.	98.6	98.2			
G.F.	70.7	70.2	E.P.	80.0	80.0			
D.S.	77.4	77.4	E.V.	80.9	80.9			

considerable amount of the I-131 has entered the oedema fluid at the time thyroid plasma clearance rates were measured; i.e. 4 hours after the administration of the dose. If this were so the plasma concentration of I-131 at this time should be lower than normal but as is shown in Table XVIII this was not the case. As can be seen in Table XVII the inorganic plasma iodide level is elevated somewhat and therefore dilution of the tracer dose with I-127 does occur. However it can be seen that this dilution does not explain all of the depression of I-131 thyroid clearance for the amount of I-127 that is calculated as entering the thyroid per hour is somewhat less than normal (Table XVII). However as the fasting plasma I-127 is somewhat higher than for the control individuals, the interchange of iodine molecules between the plasma and thyroid would be at a faster rate following Le Chatelier's principle even though thyroid function remained the same. Therefore as the rate of I-127 exchange between plasma and thyroid was actually somewhat less than normal (Table XVII) it is safe to say that thyroid function was diminished in these individuals. This would be corroborated by the low normal protein-bound iodine levels in most patients (Table II). As the mean age of these individuals is 69.4 (Table II), one might expect some degree of thyroid hypofunction which is a normal finding in old age according to Perlmutter and Riggs (40).

It is realized in this small series of 7 cases it would be presumptuous to state that one test or another was the more accurate

test of thyroid function in patients with congestive heart failure but it is felt that the I-127 thyroid uptake rate will offset the dilution artefact and will give the most reliable expression of thyroid function in these individuals. However as this test is rather time-consuming it is felt that if it is realized that the 26 hour in vivo thyroid uptake will be somewhat low because of dilution artefact this estimation will give a good representation of true thyroid function.

SUMMARY

In the 7 patients studied while in congestive heart failure due to various heart pathology it was noted that there was retention of a given dose of radio-iodide. This was demonstrated by a diminished renal clearance of I-131 and by an increase in the 26 hour plasma concentration of the isotope. However it was noted that the percentage tubular reabsorption of I-131 was less than that for the control subjects and that the retention of I-131 was due solely to a decrease in the filtration rate. In normal dogs on low salt diets and therefore retaining sodium and chloride the tubular reabsorption of iodide is almost complete, whereas in patients in congestive heart failure who are also retaining salt tubular reabsorption of I-131 is less than normal.

In patients with heart failure the thyroid uptake of I-131 continued to rise until the second or third day after the administration of the dose in marked contrast to the control subjects.

The thyroid plasma clearance rates and A. R. for patients in congestive heart failure were below the accepted range for normal subjects. This was explained partly as an artefact due to dilution of the I-131 with high plasma inorganic iodide concentrations. However it was thought that these patients showed some degree of thyroid hypofunction because the calculated stable iodide thyroid uptake was less than normal. This was explained not on the heart disease but rather on the age of the patients concerned.

Supporting the suggestion of thyroid hypofunction was the low mean protein-bound iodine concentrations which, however, might be due to low plasma albumin in some cases and to hydraemia in others.

CHAPTER VII

GENERAL DISCUSSION PERTAINING TO PATIENTS WITH RENAL DISEASE AND TO PATIENTS IN CONGESTIVE HEART FAILURE

As heart disease and kidney disease have certain things in common in respect to the abnormal handling of a tracer dose of radio-iodide it was thought that a discussion of the similarity and differences in the manner in which radio-iodide is metabolized in patients with these two diseases was indictaed.

It can be seen from Tables IV & XIII that although the kidney radio-iodide clearance rate is depressed in both of these groups the degree of depression is much more marked in patients with renal disease. Concomitant with this is the more marked depression of glomerular filtration rate in patients with renal disease (Tables I & III). As the plasma concentration of I-131 at the time of study was roughly the same in both groups the amount of I-131 filtered per unit time was considerably less in the 'renal' group. However as has been noted previously, patients with renal disease reabsorbed a greater percentage of the tubular load than the control group, whereas patients with congestive heart failure reabsorbed less. Therefore two factors tend to widen the gap between the radio-iodide clearance rates for patients with renal disease and patients with heart failure.

In an attempt to explain the increased I-131 tubular reabsorption in renal disease and the decreased I-131 tubular reabsorption in heart failure the following hypothesis is presented. As has been shown by Platt in a fairly large series there is a decrease in the percent reabsorption of the sodium tubular load in patients with renal failure (32). This has been confirmed in 2 patients with renal failure in this series (Table VII). There also appears to be a similar trend with chlorides in these 2 patients (Table VII). It has been noted by various workers that in congestive heart failure there is retention of sodium and chloride and that this is brought about largely by an increase in the percent reabsorption by the kidney tubules (41, 42). In contrast to this it is noted in this series that in renal disease a greater than normal percentage of I-131 is reabsorbed whereas in heart failure a less than normal percentage is reabsorbed (Tables VI & XV). In order to explain this it is proposed that iodide, sodium and chloride are handled by the same portions of the tubular apparatus. In renal failure the tubules for some reasoh, possibly a deficiency of mineralo-corticoids or an excess of chloruetic activity of the posterior pituitary reabsorb less of the filtered sodium and chloride than normal. Therefore less tubular work, in respect to these electrolytes, is expended. This work decrease then results in an increase in the available tubular energy in respect to iodide and therefore results in increased iodide reabsorption. Likewise in heart failure more tubular energy is required to reabsorb the

larger amounts of sodium and chloride resulting in less energy being available for iodide reabsorption. It is realized of course that this hypothesis only holds if sodium or at any rate chloride and iodide are handled by the same portions of the tubular system and that chloride and sodium plus iodide reabsorption always taxes that portion of the tubular apparatus to a maximum. It is very interesting in this regard that 2 patients, B.S. and H.A. who had severe renal disease but who were also in congestive heart failure at the time of study and therefore retaining salt, reabsorbed 67% and 72% of the tubular iodide load both of which are below the mean value for normal subjects and far less than that noted for patients in renal failure alone (Table VI). One of these patients--H.A. was shown to be reabsorbing 99% of the tubular sodium load.

The mean 26 hour plasma concentration of I-131 for patients with heart failure was less than that for patients with renal disease (Tables V & XIV). This is a reflection, at least in part, of the decreased retention of I-131 by patients with heart failure as shown by radio-iodide clearance rates as compared to patients with renal disease (Tables IV & XIII). Although it has been stated that at 4 hours after the administration of the dose of I-131 there was little evidence that any large amount of the isotope had entered the oedema fluid in patients with heart failure it is a distinct possibility that the lower 26 hour radio-iodide plasma concentrations noted for patients with heart failure might be partly due to loss

of I-131 into oedema fluid. Hydraemia of the circulation blood, as is claimed by various workers, might also play a part in the lower 26 hour plasma concentration of I-131 in patients with heart failure.

The thyroid plasma clearance rates of I-131 are considerably less for the group of patients with renal failure than for the group in congestive heart failure (Tables IX & XVI). However the dilution artefact is much greater for patients with renal disease than for those in heart failure as shown by the plasma I-127 concentration (Tables XI & XVII). It might be expected then that the calculated I-127 uptake by the thyroids of each group would be similar. As is shown in Tables XI & XVII this was not the case but rather patients with renal disease, because of their high plasma I-127 concentration, picked up greater than normal amounts of I-127 whereas patients in heart failure picked up less. It has been proposed that the reason the patients in congestive heart failure picked up less I-127 than normal was because of a mild degree of thyroid hypofunction which was due, not to heart failure per se, but to the ages of the patients concerned (40).

It has been stated previously that in patients with renal failure the 26 hour thyroid uptake gives a figure which, although low, is probably nearest to the actual thyroid function in these individuals. The I-127 thyroid uptake rate was shown to be high in these individuals and was presumed to be due to the high plasma concentration of I-127 (Table II). It was felt that this increased

iodine uptake by the thyroid did not result in increased output of hormone for these patients were clinically euthyroid and their protein-bound iodine concentrations were not high (Table I). Corroborative of this is that on analysis of thyroids from 2 patients dying in renal failure the inorganic iodine content was considerably higher than normal but the organic iodine content was within normal limits.

As elevation of plasma I-127 concentration in patients with congestive heart failure was only slightly increased above the normal it was felt that the I-127 uptake rate would give the best estimation of thyroid function in patients with heart failure (Table XVII). However this estimation has the drawback of being time-consuming. The 26 hour thyroid uptake (Figure IV) appears to give a fairly good approximation of thyroid function although the results are on the low side probably because of dilution artefact and in this series also because of the patients ages (40). It is felt however that in ruling out hyperthyroidism in patients with congestive heart failure this simply performed test would be adequate as high results would not be expected outside of increased thyroid function. In ruling out myxoedema the 26 hour thyroid uptake should be adequate if it is kept in mind that in congestive heart failure this figure is low even with normal thyroid function.

CHAPTER VIII

CONCLUSIONS REACHED ON THE EFFECT OF CONGESTIVE HEART FAILURE AND RENAL DISEASE ON THE THYROID UPTAKE AND URINARY EXCRETION OF I-131

In patients with renal disease and in patients with congestive heart failure there is a decrease in the rate of urinary excretion of a tracer dose of I-131. In renal dysfunction this is brought about by a decrease in the glomerular filtration rate and by an increase in the tubular reabsorption of I-131. In congestive heart failure, however, the decreased urinary excretion of I-131 is solely due to a decreased filtration rate for the tubular reabsorption of I-131 is less than normal.

While the tubular reabsorption in renal disease is greater than normal for I-131, it is less than normal for sodium and chloride; whereas in congestive heart failure the tubular reabsorption for I-131 is less than normal and for sodium and chloride greater than normal.

This decreased urinary excretion resulted not only in retention of a given dose of I-131 but also in an increase in the plasma concentration of stable iodide. As the decrease in urinary excretion is more marked in renal disease than in congestive heart failure, there is a greater retention of I-131 and of its stable isotope.

In renal disease and in congestive heart failure the I-131 thyroid uptake curve is flatter than normal but attains normal

values at 26 hours and continues to rise, not reaching its asymptotic level until 2-3 days after the administration of the tracer dose. The flattening of the I-131 thyroid uptake curve is reflected in a decrease in the thyroid clearance rate and accumulation rate of I-131. In renal disease this decrease in the rate of I-131 uptake by the thyroid is due to a dilution of the radioactive isotope with high plasma concentrations of stable iodide; for the calculated stable iodide uptake is actually greater than normal. In congestive heart failure the decrease in the thyroid uptake of I-131 appears to be due partly to dilution of the radioactive isotope with high plasma concentrations of stable iodide and also to some degree of thyroid hypofunction which is explained on the senescence of the patients concerned rather than on heart failure.

As there is retention of iodide in renal disease and in congestive heart failure the thyroid is presented with higher concentrations of I-131 for longer periods of time than is normal and therefore continues to pick up past the 26 hour period.

There is no evidence that any of the patients with renal disease had any disturbance in hormone formation. As has been stated, the ages of the patients with congestive heart failure are compatible with some degree of thyroid hypofunction but there is no evidence that heart disease per se results in any decrease in thyroid activity.

In patients with renal disease and in patients with congestive heart failure the thyroid clearance rates, A.R. (Keating),

R.E.R. (Keating), E.R.D.R. (Keating) and the 48 hour urinary excretion of I-131 all give fallacious results.

The 26 hour in vivo thyroid uptake of I-131 is a simply performed test and gives a figure which is thought to be the best indication of true thyroid function in patients with renal disease and in patients with congestive heart failure.

REFERENCES

1. Orr, J. B. and Leitch, I.
Medical Research Council - Iodine in Nutrition pp 5-6, 1929.

2. Baumann.
Ztschr f. physiol. Chem. 21:319, 1896.

3. Kendall, E. C.
J. Biol. Chem. 20:501, 1915.

4. Barker, S. B. and Humphrey, M. J.
J. Clin. Endocrinol. 10:1136, 1950.

5. Marine, D. and Feiss, H. O.
J. Pharmacol. and Experim. Therap. 7:557, 1915.

6. Sturm, A.
Verhandl. d. deutsche Gesellsch f. inn. Med. 39:116, 1927.

7. Elmer, A. W.
Endocrinol. 18:487, 1934.

8. Hertz, S., Roberts, R. and Evans, R. D.
Proc. Soc. Exper. Biol. and Med. 38:510, 1938.

9. Skanse, B.
Acta Med. Scand. Supp. 235: pp17, 1949.

10. Skanse, B.
Acta Med. Scand. Supp. 235: pp54, 1949.

11. Hamilton, J. G. and Soley, M. H.
Amer. J. Physiol. 127:557, 1939.

12. Hamilton, J. G. and Soley, M. H.
Amer. J. Physiol. 127:557, 1939.

13. Perry, W. F. and Semmel, J. P.
Can. Med. Assoc. J. 62:484, 1950.

14. Werner, S. C., Hamilton J. G., Leifer, E. and Goodwih, L. D.
J. Clin. Endocrinol. 10:1054, 1950.

15. Werner, S. C., Quimby, E. H. and Schmidt, C. J.
J. Clin. Endocrinol. 9:342, 1949.

16. Myant, N. B., Pochin, E. E. and Goldie, E. A. G.
Clin. Sc. 8:1002, 1949.

17. Skanse, B.
Acta Med. Scand. Supp. 235: pp94-98, 1949.

18. Keating, F. R. Jr., Haines, S. F., Power, M. H. and Williams, M. M. D.
J. Clin. Endocrinol. 10:1425, 1950.

19. Schaler, C. R. and Takayasu, R.
Deutsches Arch. f. klin. Med. 101:33, 1910.

20. Nyiri, W.
Wein Arch. f. inn. Med. 9:511, 1925.

21. Perry, W. F. and Cosgrove, J. B. R.
Can. Med. Assoc. J. 60:602, 1949.

22. Peters, J. P. and Man, E. B.
J. Clin. Invest. 27:397, 1948.

23. Selvaag, O.
Nord. Med. 37:375, 1948.

24. Ansell, G. and Rotblat, J.
Brit. J. Radiol. 21:552, 1948.

25. Miller, E. R., Soley, M. H. and Dailey, M. E.
Amer. J. Roentgenol. 60:45, 1948.

26. Barker, S. B.
J. Biol. Chem. 173:715, 1948.

27. Barker, S. B.
Personal Communication.

28. Keating, F. R. Jr., Power, M. H., Berkson, J. and Haines, S. F.
J. Clin. Invest. 26:1138, 1947.

29. McConahey, W., Keating, F. R. Jr. and Power, M. H.
J. Clin. Invest. 28:191-198, 1949.

30. Keating, F. R. Jr., Wang, J. C., Luellen, T. J., Williams, M. M. D.,
Power, M. H. and McConahey, W. M.
J. Clin. Invest. 28:217-227, 1949.

31. Brod, J. and Sirota, J. H.
J. Clin. Invest. 27:645, 1948.

32. Platt, R.
Clin. Sc. 9:367, 1950.

33. Schales, O. and Schales, S.
J. Biol. Chem. 140:879, 1941.

34. Hawk, P., Oser, B. and Summerson, W.
Practical Physiological Chemistry, 12th ed.,
Blakiston Co., Philadelphia, 1947.

35. Riggs, D. S.
Fed. Proc. 8:328, 1949.

36. Weston, R. E., Hellman, L., Escher, D. J. W., Edelman, I. S.,
Grossman, J. and Leifer, L.
J. Clin. Invest. 29:639, 1950.

37. Smith, H.
Lestures on the Kidney, pp35,
Waverley Press, Baltimore, 1943.

38. Mason, A. S. and Oliver, R.
Lancet 2:456, 1949

39. Stanley, M.
J. Clin. Endocrinol. 9:10, 1949.

40. Perlmutter, M. and Riggs, D. S.
J. Clin. Endocrinol. 9:430, 1949.

41. Davis, J. O. and Shock, N. W.
J. Clin. Invest. 28:1459, 1949.

42. Lotspeich et al.
Am. J. Physiol. 148:445, 1947.