THYROID FUNCTION IN NEPHROSIS [1]

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Since hypometabolism and hypercholesterolemia are common to both hypothyroidism and nephrosis, it was postulated that thyroid activity was subnormal in nephrotic patients. However, Epstein found that remarkably large doses of thyroid hormone could be given to nephrotic patients without inducing hypermetabolism (1). Such tolerance to thyroid medication is unusual among patients with true hypothyroidism. It has therefore been suggested that the hypometabolism and increased serum cholesterol in nephrosis are due not to decreased thyroid function but to other causes, as yet unknown (2).

The recent demonstration that the concentration of protein-bound iodine in the serum is reduced in nephrosis (3) has once more raised the question of whether thyroid function is impaired in this syndrome. The present study is an attempt to answer this question.

MATERIALS AND METHODS

The subjects for this study were patients in the active phase of the nephrotic syndrome with hypoproteinemia, proteinuria, and edema. All were hospitalized, eight at the Peter Bent Brigham Hospital, eight at the Presbyterian Hospital, and three at the Massachusetts General Hospital. The sex, age, and type of nephrosis are listed in Table I.

The concentration of protein-bound iodine in the serum was determined by the method of Man, Smirnow, Gildea, and Peters (4). In certain patients the same method was used for the determination of protein-bound iodine in urine. The volume of urine used for analysis was so chosen as to contain approximately 0.4 gm. of protein. The urinary protein was precipitated with acid zinc sulfate and sodium hydroxide, using the same quantities of these reagents as for 6 ml. of serum. In order to obtain complete precipitation, the pH of the suspension of precipitate was carefully adjusted to between 7.0 and 7.5. When the concentration of protein was small and the aliquot of urine correspondingly large, as much as two or three times the quantities of precipitating reagents were required to avoid highly disperse precipitates. Before analysis, the precipitates were washed thrice in doubly distilled water and centrifuged.

In most patients the ability of the thyroid gland to accumulate iodine was tested by the oral administration of a tracer dose (100 microcuries or less) of radioactive iodine. The isotope with a half-life of 8.0 days, I^{131}, was obtained from the Clinton Laboratories, Oak Ridge, Tennessee. It was administered orally without added carrier. In some patients the per cent of the dose accumulated by the thyroid gland in 24 or 48 hours (uptake) was estimated by *in vivo* measurements of radioactivity in the neck. The details of the techniques used have been described (5, 6). In other patients the rate of collection (accumulation gradient) was measured by the method of Stanley and Astwood as described by Perlmutter and Riggs (7). The accumulation gradient is defined as the slope of the approximately straight line obtained when the radioactivity over the thyroid gland, expressed as counts per second, is plotted on the ordinate, against the square root of time in minutes on the abscissa.

In certain experiments thyrotropic hormone [3] was employed. Two preparations, one assaying 2.6 Evans units per mgm. and the other 4.5 Evans units per mgm., were used. The preparations were dissolved in physiological saline and injected intramuscularly in a dose of 15 mgm. every six hours for two days. The design of these experiments and of others in which d,l-thyroxine was injected intravenously will be described below under "Results."

RESULTS

The serum protein-bound iodine is subnormal in nephrosis. The concentration of serum protein-bound iodine in 16 patients with the nephrotic syndrome was distinctly subnormal: below 3.0 μg. % in 13, borderline (3.0 to 3.4 μg. %) in two, and normal (3.5 to 7.0 μg. %) in only one (Table I). The mean was 2.2 μg. %.

The ability of the thyroid gland to collect iodine

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[3] The thyrotropic hormone was kindly supplied to us by Armour and Co., Chicago, Ill.

TABLE I

Laboratory data in 19 nephrotic patients

Patient	Sex	Age	Diagnosis	Serum protein gm. %		Serum protein-bound iodine	Radioiodine		Basal metabolic rate	Serum cholesterol
				Total	Albumin		Uptake	Accumulation gradient*		
						%				mgm. %
T. E.	M	9	Nephrosis	—	1.5	1.3				400
T. K.	M	12	Nephrosis	—	3.0	3.1				425
C. L.	F	22	Nephrosis	3.7	2.2	1.8		18.0	−10%	335
J. P.	M	14	Nephrosis	3.8	1.5	2.2		9.4	−4%	474
D. H.	F	48	Nephrosis	2.5	1.0	1.7		12.2	−39%	340
S. H.	F	15	Nephrosis	3.0	1.7	2.0	32%†		−25%	750
A. M.	M	18	Nephrosis	3.2	1.5	1.8	40%†		−22%	600
F. C.	M	17	Nephrosis	3.5	2.2		55%†	19.0	−27%	316
J. C.	M	38	Nephrosis	3.4	2.2	1.8	26%†	8.0	−36%	492
G. D.	M	18	Nephrosis	3.2	0.9	0.9			−26%	755
P. O.	M	14	Chr. glom. nephrotic	5.7	2.3	3.4		5.0	−15%	176
H. D.	M	26	Chr. glom. nephrotic	3.8	2.0	1.5		0.7		595
J. H.	M	62	Chr. glom. nephrotic	3.6	2.5	2.0	75%‡			312
J. K.	M	34	Chr. glom. nephrotic	3.3	2.0	2.2	44%‡		−27%	510
M. R.	M	11	Chr. glom. nephrotic	3.7	1.6	2.1	25%†		−35%	716
F. R.	F	32	Lupus nephrosis	3.4	2.0	5.2	38%†	10.2	0%	329
V. F.	F	35	Lupus nephrosis	3.8	2.0		44%†	14.0	−10%	200
J. M.	F	20	Tridione nephrosis	3.0	1.9		38%†	10.0	−19%	562
F. A.	M	30	Amyloid nephrosis	4.3	2.0	1.9	71%‡		−26%	329
Mean		25		3.6	1.9	2.2		10.6	−21%	453

* Slope of line obtained when the counts per minute over the thyroid gland are plotted as the ordinate against the square root of the time in minutes as the abscissa. Normal range: approximately 0.4 to 10 (7).

† Per cent of a tracer dose of I^{131} in the thyroid as estimated from *in vivo* measurements 24 hours after administration. Normal range: 10% to 40% (5).

‡ Per cent of a tracer dose of I^{131} in the thyroid as estimated from *in vivo* measurements over the neck 48 hours after administration. Normal range: 17% to 58% (6). The urinary excretion of I^{131} was also measured in two patients: F.A., 15.2% in the first 24 hours, 1.7% in the second 24 hours; J.K., 35.0% in the first 24 hours, 11.4% in the second 24 hours.

is unimpaired in nephrotic patients. In 16 nephrotic patients the avidity of the thyroid gland for iodide was tested with tracer doses of I^{131} (Table I). In some patients the *rate* of collection (accumulation gradient) was measured, in others the percentage of the dose retained by the thyroid gland 24 or 48 hours after administration of radioactive iodine was determined. Both measurements were used in five patients. With but one exception (patient H. D.) the accumulation of iodide was rapid. In several of the patients the accumulation gradient was actually greater than in most normal subjects. Similarly the per cent of a tracer dose retained by the thyroid gland was either normal or, in patients J. H., F. A., R. C., V. F., greater than normal.

The basal metabolic rate tends to be low, and the serum cholesterol high in nephrosis. These well established facts are illustrated by the data in the last two columns of Table I. In 15 patients the mean BMR was − 21%. Ten of the 15 values were below − 15%. The mean serum cholesterol was 453 mgm. %; 17 of the 19 values were above 300 mgm. %.

Protein-bound iodine is lost in the urine of nephrotic patients. In four patients the urinary excretion of protein-bound iodine was measured during 24 hour periods (Table II). It varied considerably from patient to patient without any obvious relation to the degree of proteinuria. Thus patient D. H. excreted an average of 7.2 gm. of protein and 6.0 μg. of protein-bound iodine in 24 hours, while patient J. P. excreted 5.8 gm. of protein and 31.8 μg. of protein-bound iodine over the same period. In all four patients the amount of protein-bound iodine per gram of urinary protein was equal to or greater than the amount of protein-bound iodine per gram of serum protein. The ratio of these two is given in the last column of Table II under the heading "U"/"S."

Urinary protein-bound iodine increases when the serum protein-bound iodine increases. In two

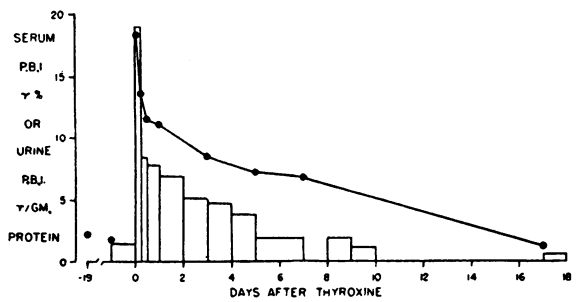

FIG. 1. NEPHROTIC PATIENT C. L., FEMALE. AGE, 22. BODY WEIGHT, 50.8 KGM.

At zero time, 7 mgm. of d,l-thyroxine were injected intravenously. The serum protein-bound iodine is represented by the solid circles. The concentration of protein-bound iodine in the urine per gram of urinary protein is indicated by the open bars.

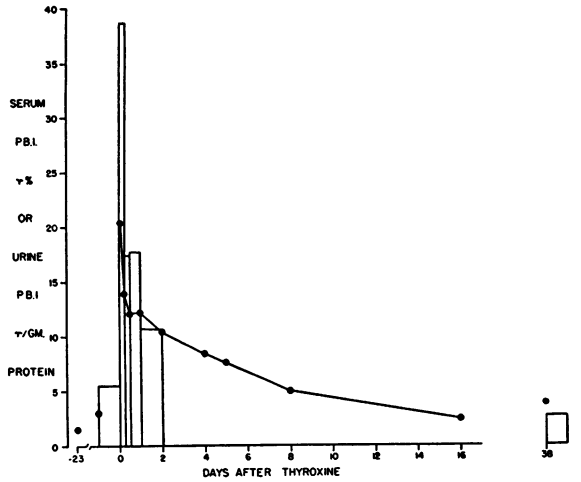

FIG. 2. NEPHROTIC PATIENT J. P., FEMALE. AGE, 13. BODY WEIGHT, 36.4 KGM.

At zero time, 5 mgm. of d,l-thyroxine were injected intravenously. The serum protein-bound iodine is represented by the solid circles. The concentration of protein-bound iodine in the urine per gram of urinary protein is indicated by the open bars.

nephrotic patients the serum protein-bound iodine was deliberately increased by the intravenous administration of d,l-thyroxine in a dose of 140 μg. per Kgm. of body weight (Figures 1 and 2). The excretion of protein-bound iodine in the urine rose immediately and then decreased as the serum protein-bound iodine fell towards the initial level. There was a better correlation between the *iodine per gram of urine protein* and the concentration of protein-bound iodine in the serum than between the *total quantity* of protein-bound iodine excreted and the serum protein-bound iodine. This suggests that the appearance of protein-bound iodine in the urine was due at least in part to the excretion of protein to which iodine was already bound, and not simply to an excretion of free thyroxin which subsequently became bound to the protein in the urine.

The rate of decrease of protein-bound iodine in the serum is not abnormally rapid after the administration of thyroxine to nephrotic patients. The time required for the serum protein-bound

TABLE II

Loss of protein-bound iodine in the urine in untreated patients with nephrosis

Patient	Serum total protein	Serum protein-bound iodine	Serum protein-bound iodine	Urine total protein per 24 hrs.	Urine protein-bound iodine	Urine protein-bound iodine	"U"/"S"
	gm. %	*μg. %*	*μg. per gm. protein (S)*	*gm.*	*μg. per 24 hrs.*	*μg. per gm. protein (U)*	
M. R.	3.7	1.8	0.49	12.9	16.2	1.25	
		2.3	0.62	22.2	22.7	1.02	
Mean	3.7	2.0	0.56	17.5	19.4	1.14	2.04
D. H.	2.5	1.7	0.68	7.3	3.6	0.50	
		2.5	1.00	8.3	6.6	0.79	
				6.0	7.9	1.31	
Mean	2.5	2.1	0.84	7.2	6.0	0.87	1.04
J. P.	3.8	3.0	0.79	5.8	31.8	5.48	6.94
C. L.	3.7	1.8	0.49	24.2	36.1	1.49	3.04
Mean of four pts.	3.4	2.2	0.67	13.7	23.3	2.24	3.26

iodine to return to initial levels following the intravenous injection of d,l-thyroxine was studied in two nephrotic patients, two patients with untreated myxedema, and one normal subject. In Figure 3, the increase of the serum protein-bound iodine above the initial control concentration is plotted on a logarithmic scale against time on an arithmetic scale. The curves are quite similar in shape to the curve for radioactive d,l-thyroxine in the serum of a cretin studied by Albert and Keating (8). The relatively rapid initial decrease of the concentration during the first 12 hours was probably due to the distribution of thyroxine from the blood stream to the tissues. The subsequent slow decline of concentration was presumably dependent upon the rate of utilization and excretion of thyroxine after distribution equilibrium had been attained. This second rate of decline was no more rapid in the nephrotic patients than in the normal subject. The time needed for the concentration of protein-bound iodine to decrease 50% was approximately 4.3 days both for the normal subject and for the nephrotic patients. This agrees well with the biological half-life of radioactive thyroxine, 3.8 days, in Albert's and Keating's patient with *treated* hypothyroidism. In contrast, the time required for a 50% decrease in concentration in our patients with *untreated* hypothyroidism was 8.3 days.

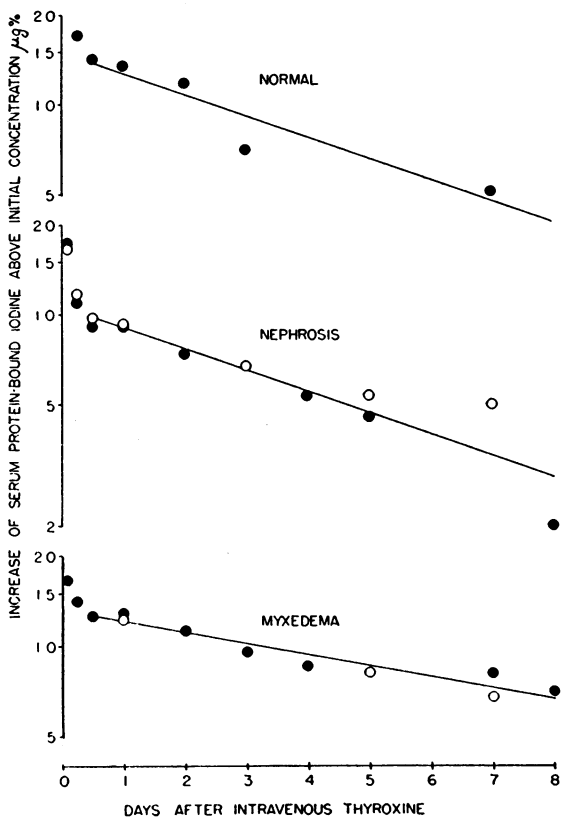

FIG. 3. THE RATE OF DECREASE OF SERUM PROTEIN-BOUND IODINE AFTER THE INTRAVENOUS ADMINISTRATION OF D,L-THYROXINE

The increase in serum protein-bound iodine above the initial control concentration is plotted on a logarithmic scale against time in days after the injection of thyroxine. In determining the straight lines by the method of least squares, the points at times less than 12 hours have been disregarded, and the data from patients with the same diagnosis have been pooled.

Top curve: Normal male, age 20, dose of thyroxine 10 mgm. *Middle curve:* Open circles = nephrotic patient C. L., female, age 22, dose of thyroxine 7 mgm.; solid circles = nephrotic patient J. P., female, age 13, dose of thyroxine 5 mgm. *Bottom curve:* Open circles = patient with pituitary myxedema, age 48, dose of thyroxine 5 mgm.; solid circles = patient with spontaneous myxedema, female, age 71, dose of thyroxine 5 mgm. The slopes of the curves indicate the following times for the concentration to decrease by 50%: Normal, 4.3 days; Nephrosis, 4.3 days; Myxedema, 8.3 days.

Thyroid activity in nephrotic patients decreases in response to an excess of thyroid hormone. In the two nephrotic patients and the one normal subject given thyroxine, the avidity of the thyroid gland for iodine as measured by the accumulation gradient decreased markedly after the administration of thyroxine (Table III). In patient J. P. the gradient decreased from 9.4 before thyroxine to 0.7, seven days after thyroxine, and was still only 2.5 one month after thyroxine. Presumably this decrease was due to inhibition of the output of thyrotropic hormone by the anterior pituitary gland in response to an excessive supply of thyroid hormone (9).

In nephrosis the thyroid gland is able to respond to thyrotropic hormone. Two patients with ne-

TABLE III

Effect of I.V. thyroxine upon I^{131} accumulation gradient

Subject	Gradient before treatment	Gradient 7 days after treatment
Nephrotic J. P.	9.4	0.7
Nephrotic C. L.	18.0	3.0
Normal R. W.	11.0	3.0

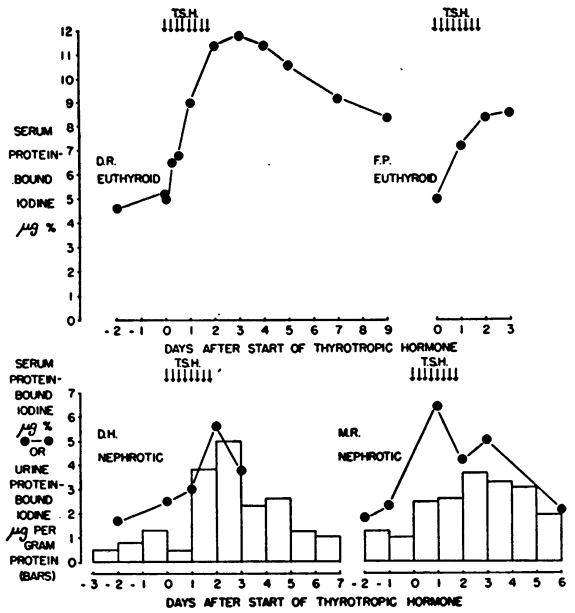

FIG. 4. THE RESPONSE OF NEPHROTIC PATIENTS AND OF NORMAL SUBJECTS TO THYROTROPIC HORMONE

Each of the arrows marked "TSH" indicates the intramuscular injection of 15 mgm. of Armour's thyrotropic hormone. The preparation administered to D. R. contained 4.5 Evans units per mgm. The preparation used in the other three subjects contained 2.6 Evans units per mgm.

D. R., normal male, age 37. F. P., euthyroid male, age 66, recovering from an abdominal operation. D. H., nephrotic female, age 48. M. R., nephrotic male, age 11.

phrosis were given 15 mgm. of Armour's thyrotropic hormone intramuscularly every six hours for two days (Figure 4). In both patients the serum protein-bound iodine and the urinary protein-bound iodine rose significantly during the administration of thyrotropic hormone. The response of the serum protein-bound iodine in two euthyroid male subjects given thyrotropic hormone is also depicted in Figure 4. The thyrotropic hormone given to one of the normal subjects, D. R., was a different preparation from that used in the nephrotic patients, although in terms of units the dose (approximately 4.5 Evans units per Kgm. of edema-free body weight per day) was about the same as in patient M. R. In the normal subjects the elevation in protein-bound iodine appeared to be sustained longer than in the nephrotic patients. However, since little is known about normal variations in the response of different subjects to thyrotropic hormone, the significance of this difference between normal and nephrotic cannot be interpreted.

A comparatively brief period of treatment with l-methyl-2-mercaptoimidazole may inhibit the response of the nephrotic patient to thyrotropic hormone. The ability of thyrotropic hormone to elicit a rise of serum protein-bound iodine during a brief period of treatment with 1-methyl-2-mercaptoimidazole was tested in one patient with nephrosis and in one euthyroid patient (Figure 5). In both patients, 10 mgm. of 1-methyl-2-mercaptoimidazole, three times a day, produced an almost complete block of thyroid hormone synthesis as indicated by a greatly diminished uptake of radioactive iodine. During the first eight or nine days of treatment, the serum protein-bound iodine did not change significantly in the patient with nephrosis, and fell only slightly in the euthyroid patient. While 1-methyl-2-mercaptoimidazole was continued, each subject was given 15 mgm. of the same preparation of Armour's thyrotropic hormone intramuscularly every six hours for two days. The serum protein-bound iodine in the euthyroid patient promptly rose from 3.4 to 7.9 μg. %. However, in the nephrotic patient, it not only failed to rise appreciably, but actually fell somewhat the day after thyrotropic hormone was discontinued. These observations suggest that when the synthesis of new hormone was blocked for a few days,

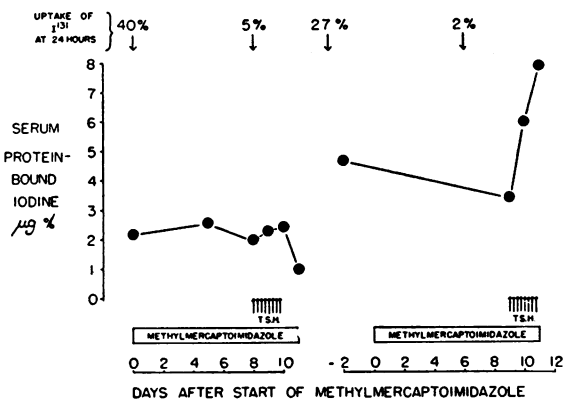

FIG. 5. THE RESPONSE OF A NEPHROTIC SUBJECT (LEFT) AND A EUTHYROID SUBJECT (RIGHT) TO THE ADMINISTRATION OF THYROTROPIC HORMONE DURING A BRIEF PERIOD OF TREATMENT WITH 1-METHYL-2-MERCAPTOIMIDAZOLE

The dose of 1-methyl-2-mercaptoimidazole was 10 mgm. three times a day. Each arrow marked "TSH" indicates the intramuscular injection of 15 mgm. of Armour's thyrotropic hormone containing 2.6 Evans units per mgm.

too little hormone remained in the thyroid gland of the nephrotic patient to permit a rise of the serum protein-bound iodine in response to thyrotropic hormone.

The thyroid gland is not usually enlarged in nephrosis. Thyroid enlargement was not noted in any of the patients in the present series.

DISCUSSION

The results of the present study suggest several hypotheses concerning thyroid function in nephrosis.

Although abnormal loss of thyroid hormone in the urine occurs, this finding does not of itself adequately explain all the observed facts. In four nephrotic patients the greatest loss of protein-bound iodine was 36 μg. in 24 hours. In two cases, Peters and Man observed a loss of 16 to 48 μg. (3). Since patients with myxedema require for replacement therapy about 100 μg. of iodine as l-thyroxine (10), and calculations in the euthyroid individual based upon radioactive iodine uptake and iodide excretion studies indicate a normal daily secretion of 50 μg. of hormonal iodine (11), it is apparent that significant losses of hormonal iodine may, but do not always, occur in the nephrotic. Further, in two patients following intravenously administered thyroxine, urinary loss in 48 hours was only 6.7 and 6.3% of the dose. These observations coupled with an apparently normal rate of disappearance of serum protein-bound iodine make it improbable that the urinary loss of hormone is the major problem with regard to the thyroid status in these patients.

If the loss of hormone should quantitatively represent an important mechanism depriving the tissues of thyroid substance, a compensatory increase in the secretion of pituitary thyrotropic hormone would be expected. Providing that the resulting hyperactivity of the thyroid gland could keep pace with the hormone loss, the concentration of serum protein-bound iodine would be restored to normal and, depending upon the degree of hyperactivity necessary for restoring this balance, thyroid enlargement might become evident. In fact, however, the concentration of protein-bound iodine in the serum remains low, and goiter has not been noted in patients with nephrosis. Thus, if this urinary loss were quantitatively significant one would have to postulate an additional pituitary or thyroid deficiency to explain the consistently low serum levels of hormone.

The possibility of inadequate secretion of thyrotropic hormone in nephrosis was considered. The avidity of the thyroid gland for radioactive iodine was normal or increased in all cases studied. Since there is good evidence that the capacity to accumulate iodide is dependent upon a normal supply of thyrotropic hormone, a pituitary deficiency seems unlikely. Further evidence that a normal thyrotropic hormone mechanism exists may be found in the response of the nephrotic to exogenously administered thyroxine, both in terms of a depression in radioactive iodine uptake and in the clinical tolerance to the drug. Finally, the behavior of the nephrotic subject to combined mercaptoimidazole and thyrotropic hormone therapy suggests that thyroid hormone stores are small and being turned over rapidly. A similar response has been reported in thyrotoxic patients (12). Since the ability of the thyroid gland to release thyroid hormone is also considered to be dependent upon the thyrotropic hormone, *a deficiency of thyrotropic activity in the nephrotic appears improbable.*

No indications of a specific thyroid gland abnormality or enlargement have been observed in the patients studied. The thyroid gland apparently can respond to exogenous thyrotropic hormone stimulation, though the quantitative aspects of the response as compared with the normal are difficult to evaluate. In addition, the thyroid gland can take up and accumulate radioactive iodine as well as or better than normal. The possibility that this latter avidity is associated with an iodine deficiency seems unreasonable in view of the abundant iodine supply in food and water in this region and the absence of an increased iodide clearance by the kidney. Indeed in J. K., in whom the urinary excretion of radioactive iodine was measured, it was slower than normal with a disproportionately large excretion in the second 24 hours (footnote, Table I). Further, iodide deficiency without some degree of thyroid enlargement would be extremely unusual.

Wolbach and Blackfan described extraordinary pathological changes in the thyroid glands of two children with nephrosis who came to autopsy (13). There was complete loss of colloid, desquamation and necrosis of the acinar epithelium, and increased

vascularity. Such extensive changes could hardly be compatible with normal thyroid function. Yet it seems likely that the histological picture described by Wolbach and Blackfan is exceptional. We are not aware of any subsequent report of similar pathological changes. Furthermore, no abnormalities of the thyroid gland were found among 10 patients with nephrosis who came to autopsy at the Babies Hospital in New York between 1935 and 1950.

It is clear, then, that a low serum protein-bound iodine must be explained despite the absence of obvious hypofunction of the thyroid or pituitary in nephrosis. Throughout the preceding discussion the tacit assumption has been made that the triad of low serum protein-bound iodine, low basal metabolic rate, and high serum cholesterol in nephrosis indicate a decreased supply of thyroid hormone to the tissues. This assumption may well be erroneous. Attention must be directed to the paucity of clinical evidence for hypothyroidism in nephrosis, to the differences between the lipemia of nephrosis and of myxedema, and to the tolerance of nephrotic patients for exogenous thyroid hormone which is certainly not characteristic of true hypothyroidism (3).

Careful consideration must therefore be given to the hypothesis that *thyroid function and the supply of hormone to the tissues in nephrosis may be normal, and that the low concentration of protein-bound iodine in the plasma is due to the change in concentration or binding capacity of the plasma proteins in nephrosis.* This hypothesis implies that when plasma protein is low, or is altered so that it is no longer able to bind thyroid hormone normally, the ability of the peripheral tissues to clear hormone from the blood stream increases. Although the circulating thyroid hormone, presumably thyroxine (14), is rather firmly bound to the proteins of plasma, it is quite possible that a fraction, undetectable by present analytical methods, is unbound. If there exists an equilibrium between protein, free thyroxine, and protein-bound thyroxine which follows the law of mass action, then a reduction in the concentration of plasma protein to which thyroxine is bound would necessitate an increase in the proportion of free thyroxine. If it be further assumed that thyroxine can traverse the cell wall and reach its site of action only in the unbound state, then an increase in the concentration of free thyroxine might favor a greater than normal rate of entry of hormone into the cells. *Hypoproteinemia would thus permit a normal supply of thyroid hormone to be carried to the tissues despite a decreased concentration of protein-bound hormone in the blood stream.*

Goldstein (15) has pointed out that the assumptions involved in this argument are not necessarily invalidated by failure to demonstrate dissociation of the thyroxine protein complex during prolonged dialysis *in vitro* (16). The occurrence of small quantities of free thyroxine in normal urine (17) suggests that traces of unbound thyroxine may indeed be present in plasma.

The hypothesis just advanced is analogous to the explanation offered by McLean and Hastings for the dependence of serum calcium on serum protein concentration (18). The parathyroid glands normally maintain a reasonably constant concentration of *ionized* calcium in the serum. When the concentration of ionized calcium is held constant, the concentration of *protein-bound* calcium varies directly with the protein concentration.

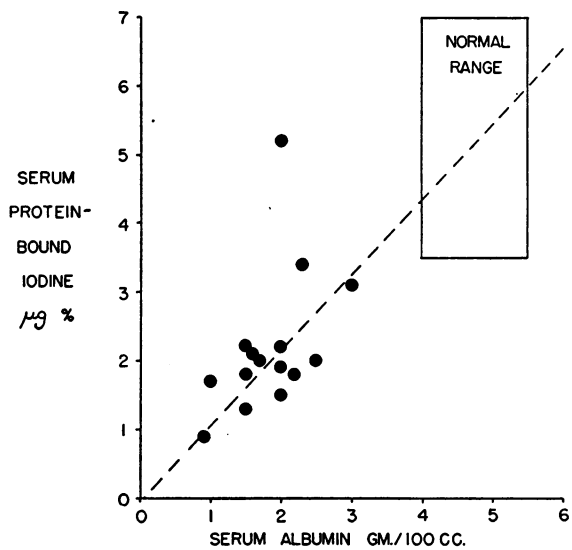

FIG. 6. THE RELATIONSHIP BETWEEN THE CONCENTRATIONS OF PROTEIN-BOUND IODINE AND OF CRUDE SERUM ALBUMIN IN THE SERUM OF PATIENTS WITH NEPHROSIS

Each circle represents a single patient. The broken line is intermediate between the lines of regression of albumin on iodine and of iodine on albumin. In calculating these regression lines by the method of least squares, the one circle within the normal range of protein-bound iodine was neglected. For comparison the approximate normal range is depicted as a rectangle.

Similarly, if the concentration of *free* thyroxine is normally kept within narrow limits by the homeostatic balance between thyroid and anterior pituitary, the concentration of *protein-bound* thyroxine should vary directly with the concentration of the thyroxine-binding groups of plasma proteins. There is evidence that most of these groups are in the albumin fraction when the usual clinical methods for the separation of serum protein into albumin and globulin are employed (16). In Figure 6, the concentration of protein-bound iodine in our patients with nephrosis has been plotted against the concentration of serum albumin. If the single normal value for protein-bound iodine (patient F. R.) is excluded, there is a highly significant correlation between these two variables. In the nephrotic patients, the ratio of mean serum albumin (in gm. %) to mean serum protein-bound iodine (in μg. %) was $1.7/1.9 = .89$. The ratio of the corresponding mean values for normal subjects is approximately $4.8/5.1 = .94$. The similarity of these ratios is consistent with the hypothesis under discussion.

The observed facts—the low serum protein-bound iodine, the normal uptake of radioactive iodine, the absence of goiter, the response to thyrotropic hormone, the lack of clinical evidence for hypothyroidism, and the tolerance of nephrotic patients to exogenous thyroid hormone—are all consistent with a euthyroid state in individuals with hypoproteinemia. However, the hypothesis by itself does not explain the failure of thyrotropic hormone to produce a rise in serum protein-bound iodine in the nephrotic patient treated with mercaptoimidazole (Figure 5), nor the increased avidity of the thyroid gland for iodine. These observations suggest that in nephrosis the quantity of hormone stored in the thyroid gland may be decreased. It seems probable that the continuous loss of hormone in the urine (both protein-bound and free) may gradually deplete the gland of preformed hormone. Such depletion must ultimately reduce the effective level of hormone in the serum so that a *slight compensatory increase in thyroid activity* would be required to restore the normal supply of hormone to the tissues. This state can be achieved without sufficient growth of the gland to produce a palpable goiter, but with an abnormally rapid and extensive uptake of radioactive iodine.

If, in nephrosis, the tissues actually receive an adequate supply of thyroid hormone despite a decreased concentration in the blood stream, deficient thyroid function cannot be held responsible for the subnormal metabolic rate. The frequent association of presumably normal thyroid activity and low basal metabolism in anorexia nervosa (3) has been noted. Similar discrepancies are often encountered among patients with partial hypopituitarism, hypogonadism (19) and among patients maintained on the Kempner rice diet (20). Adequate thyroid function seems to be necessary, but not sufficient, for the maintenance of a normal basal metabolic rate. It may be that in nephrosis the severe protein deficiency itself limits the basal rate of metabolism.

SUMMARY AND CONCLUSIONS

In 16 patients with active nephrosis the serum protein-bound iodine was low, and the serum cholesterol high. The basal metabolic rate was often subnormal even when calculated on the basis of edema-free weight. However, the uptake of radioactive iodine by the thyroid gland was normal or greater than normal, and there was a definite rise in the serum protein-bound iodine in response to thyrotropic hormone. In one patient this response was eliminated by treatment with mercaptoimidazole before and during the injection of thyrotropic hormone.

The results of this study support the supposition that thyroid function in nephrosis is essentially normal and that neither anterior pituitary failure nor inability of the thyroid gland to manufacture thyroid hormone in adequate amounts accounts for the low serum protein-bound iodine. Although protein-bound iodine was lost in the urine, it usually represented but a small portion of the estimated normal daily secretion of thyroid hormone. Furthermore, although the protein-bound iodine in the urine increased when the serum protein-bound iodine was raised by the intravenous administration of thyroxine, the urinary loss during the first two days amounted to only about 6% of the administered dose, and the rate of decrease of the serum protein-bound iodine after thyroxine was no greater than in a normal subject. It seems improbable that the urinary loss of hormone can by itself account for the subnormal concentration of protein-bound iodine in the serum.

Arguments are advanced in favor of the hypothesis that in nephrosis the decreased concentration of protein in the plasma accounts for the low serum protein-bound iodine and permits the transport and delivery of a normal supply of thyroid hormone to the tissues with a decreased concentration of hormone in the blood stream. In certain patients with nephrosis the thyroid gland may actually become somewhat hyperactive in order to compensate for the continuous loss of hormone in the urine.

The subnormal basal metabolic rate cannot be ascribed to hypothyroidism, but must be due to some other factor, perhaps the marked protein deficiency which occurs in nephrosis.

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