THE EFFECT OF LARGE DOSES OF DESICCATED THYROID ON THE DISTRIBUTION AND METABOLISM OF ALBUMIN-I^{131} IN EUTHYROID SUBJECTS

By MARCUS A. ROTHSCHILD,[1] ARTHUR BAUMAN,[2] ROSALYN S. YALOW, AND SOLOMON A. BERSON

(From the Radioisotope Service, Veterans Administration Hospital, Bronx 68, N. Y.)

(Submitted for publication August 3, 1956; accepted November 29, 1956)

It has been observed that I^{131} labeled human serum albumin, administered intravenously to normal man, is ultimately distributed between extravascular tissues and plasma in the approximate ratio of 60:40 (1, 2). This ratio is not appreciably altered in heart failure with edema (2), but may be increased somewhat in hepatic cirrhosis with ascites (1). One of the highest extravascular-intravascular ratios ever observed in this laboratory was in a patient with myxedema, in whom 73 per cent of the iodinated albumin remaining within the body at distribution equilibrium was in the extravascular spaces (2). The high extravascular albumin content in myxedema may be related to increased skin thickness since it has been shown that skin contains a disproportionately large fraction of the total extravascular albumin (3). It therefore seemed of interest to evaluate whether extravascular-intravascular shifts of serum albumin could be initiated in euthyroid subjects by the administration of large doses of thyroid hormone.

It had also been observed previously that albuminuric subjects do not generally compensate for renal losses by an increase in the rate of albumin synthesis but do so rather by a decrease in the rate of albumin catabolism (2). Because the possibility of hepatic damage in nephrotic subjects has been suggested (4), it also seemed of interest to evaluate whether subjects with normal liver function would respond with an increase in the rate of albumin synthesis to the increased rate of albumin degradation anticipated in response to excessive thyroid hormone stimulation.

METHODS

Nine male patients at the Veterans Administration Hospital, Bronx, New York, were subjects of this study. The illnesses responsible for hospitalization are given in Table I. There was no suspicion of thyroid disease nor detectable proteinuria in any of the patients. Seven subjects were maintained on a regular hospital diet, ad libitum, throughout the study. Two subjects (R. W. and S. K.) received protein supplements of 90 gm. per day in addition to the regular diet.

The distribution and metabolism of albumin were studied by means of I^{131} labeled human serum albumin. Following the intravenous administration of albumin-I^{131}, observations of plasma and urinary I^{131} were made for a control period of 15 to 22 days, following which, observations were continued for another 13 to 22 days while the subjects received 12 to 18 grains of desiccated thyroid, U.S.P., per day (Figure 1). For the purpose of reevaluating the distribution of albumin at the end of this period, a second dose of albumin-I^{131} was administered and observations were continued for another 9 to 14 days during continuing thyroid therapy except in patient D. C. in whom thyroid hormone was discontinued at the time of administration of the second dose of albumin-I^{131}.

The iodinated albumin used in these experiments was prepared according to methods previously described (1) and contained approximately one iodine atom per protein molecule. These preparations have previously been observed to undergo a uniform rate of metabolic degradation *in vivo* (1, 2). Since it has been shown that I^{131} labeled albumin of high specific activity may be damaged sufficiently by radiation to result in rapid *in vivo* degradation (5), the albumin-I^{131} employed in this study was prepared with relatively low specific activity (< 21.5 μc. per mg.). Each patient received a total of 150 to 250 μc. intravenously in 2 injections. Lugol's solution, 10 drops 3 times a day, was administered daily to block thyroidal uptake of I^{131}. Heparinized blood samples were taken without tourniquet stasis 15 minutes, 2 hours, and 6 hours after injection, and at almost daily intervals thereafter. Twenty-four-hour urine collections were obtained daily except in an occasional instance when a pooled weekend urine was collected. Plasma and urine samples were assayed for radioactivity in a well type scintillation counter with a sensitivity of 1.0×10^6 counts per min. per μc. I^{131} above a background of approximately 200 counts per min. Total serum protein concentration was determined by the Kjeldahl method and serum albumin concentration was determined by the method of Kingsley (6) at 3 to 7-day intervals throughout the period of study.

[1] Dazian Foundation Fellow, present address: Veterans Administration Hospital, Manhattan.

[2] National Heart Institute Research Fellow.

TABLE I

Data on the distribution and metabolism of albumin before and during the administration of desiccated thyroid

Lot of albumin received	Subject	Diagnosis	A: Plasma concentration (*gm./100 ml.*) Total protein Cont.*	Exp.†	B: Albumin Cont.	Exp.	Plasma volume (*ml.*) Cont.	Exp.	C: Albumin degraded daily (*gm.*) Cont. P‡	U‡	Cl‡	Exp. Cl	D: Duration of thyroid therapy (*days*)	E: Albumin degraded in excess of similar control period (*gm.*)	F: TEA§ (*gm.*) Cont.	Exp.	G: TEA loss (*gm.*)	H (E–G): Net synthesis of albumin (*gm.*)	I: Albumin partition (*gm.*) Intravascular Cont.	Exp.	Extravascular Cont.	Exp.
I	E. A.	Psoriasis	7.46	6.11	4.59	4.18	3,320	3,770	17.0	18.0	17.0	18.9	17	32	345	335	10	22	148	158	197	177
I	D. C.	Convalescent Poliomyelitis	6.99	6.41	4.53	4.36	2,620	2,970	13.4	11.1	11.2	14.8	12	43	296	305	−9	52	119	129	177	176
	F. M.	Neuro-dermatitis	7.03	6.38	4.22	4.00	3,140	3,620	15.8	14.0	14.4	18.4	16	64	343	326	17	47	133	145	210	181
II	T. M.	Multiple Sclerosis	7.02	5.88	4.89	4.00	3,660	3,760	18.6	18.2	17.6	24.6	20	140	408	353	55	85	179	150	229	203
	L. U.	Traumatic Paraplegia	7.21	6.20	4.59	3.96	2,450	2,650	18.9	17.5	17.0	19.8	13	36	309	305	4	32	112	105	207	200
	L. Z.	Keratoconus	7.11	6.44	5.18	4.82	2,770	3,070	11.2	11.7	11.3	14.9	12	43	374	360	14	29	144	148	230	212
III	P. M.	Psoriasis	6.83	5.50	4.41	4.00	2,770	3,210	16.2	14.0	13.9	18.0	22	90	265	262	3	87	122	128	143	134
IV	R. W.	Amputee	6.78	6.70	4.22	3.90	3,290	3,450	18.6	16.8	16.6	22.8	19	118	355	335	20	98	139	135	216	200
	S. K.	Convalescent Poliomyelitis	6.89	6.75	4.91	4.50	3,880	4,130	20.2	21.5	18.1	26.8	19	165	446	409	37	128	209	186	237	221
Mean values			7.03 ±0.20 (S.D.)	6.26 ±0.37	4.62 ±0.31	4.19 ±0.29	3,080	3,400	16.5	15.8	15.2	19.8	16.6	81	349	332	17	64	145	143	205	189
Per cent change				−11.0		−9.3		+10.4				+30.3					−4.9			−1.6		−7.8

* Cont.—Before desiccated thyroid administration.

† Exp.—During desiccated thyroid administration.

‡P‡U‡Cl—From plasma concentration curve, daily urinary excretion, and "metabolic clearance" techniques, respectively (see text).

§ TEA–Total exchangeable albumin.

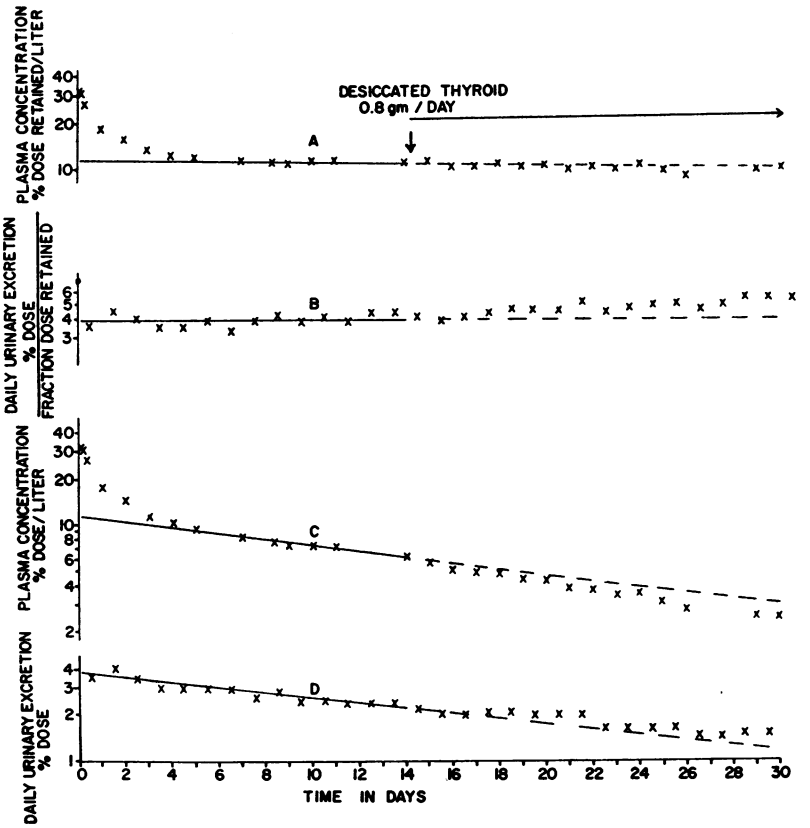

FIG. 1. TYPICAL SET OF CURVES FOR PLASMA AND URINE DATA (PATIENT F. M.) FOLLOWING ALBUMIN-I^{131} ADMINISTRATION (SEE TEXT)

Plasma volume and total exchangeable albumin (TEA) were determined by methods previously described (1).

The rate of metabolism of serum albumin was determined by several different means. Methods employing the rate constant of decrease in plasma concentration of albumin-I^{131} after distribution equilibrium or the rate of urinary excretion of I^{131} released by degradation of albumin-I^{131} have been previously described (1) and yielded essentially identical values. However, the validity of these methods depends upon the maintenance of steady state conditions. During the control period, serum albumin concentrations remained constant, and for practical purposes it may be assumed that steady state requirements were satisfied. Under these conditions the rate of synthesis is equal to the rate of degradation. However, during the experimental period of thyroid administration, changes in the distribution and the rate of degradation altered the steady state so that the validity of these methods is vitiated. Therefore, the following method, the validity of which is independent of the steady state, was employed for comparison of albumin degradation during control and experimental periods. Since radioactivity excreted in the urine in the absence of proteinuria represents I^{131} released by metabolic degradation of albumin-I^{131}, the amount degraded each day was calculated as the product of the apparent renal clearance of plasma I^{131} ("metabolic clearance") and the plasma concentration of albumin (Figure 2).[3] The total amount degraded over each period was then obtained from the sum of the daily values.[4] The quantity of albumin synthe-

[3] It has been shown previously that the urinary excretion of I^{131} reflects very closely the degradation of albumin-I^{131} owing to the very rapid rate of renal excretion of the I^{131} released by protein degradation compared to the rate of degradation itself (1). "Metabolic clearance" methods have also been used in the study of thyroid hormone degradation (7).

[4] In subject P. M. the second dose of albumin-I^{131} was administered 4 days after observations on the degradation of the first dose of albumin-I^{131} were discontinued. In subject T. M. the total exchangeable albumin was calculated from the space of distribution of albumin-I^{131} 7 days following the administration of the second dose. In both instances the mean daily albumin degradation during the last 5 days of the treatment period was assumed to continue into these 4 and 7-day periods. Although the rate of albumin degradation may have been slightly higher than the mean of the previous 5 days, this would not have introduced a significant error in the values for total albumin degraded during thyroid hormone administration.

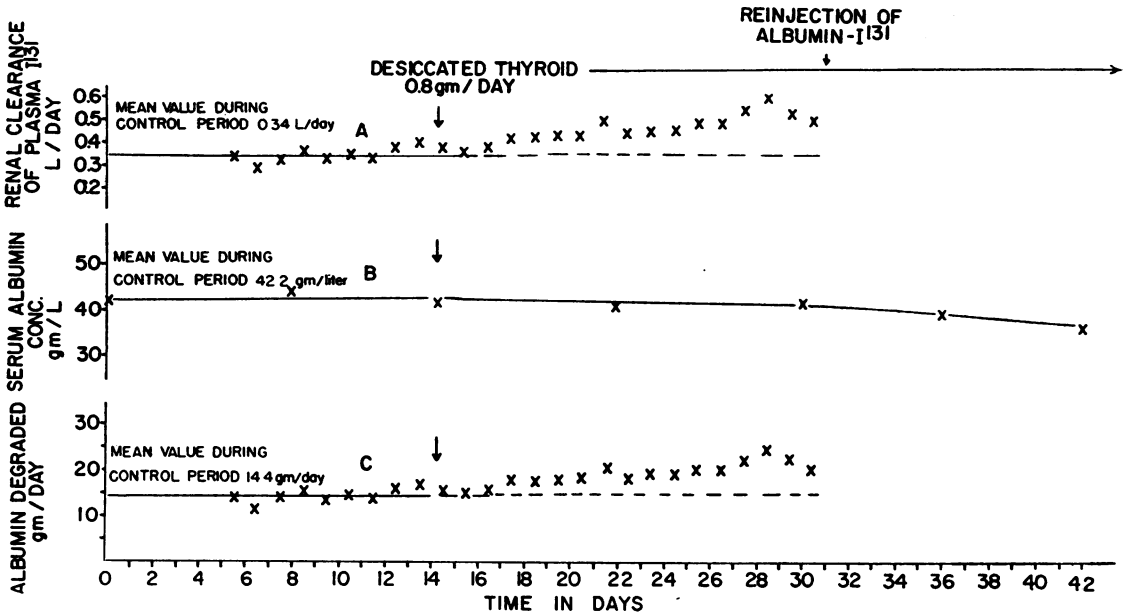

FIG. 2. PATIENT F. M. DAILY URINARY CLEARANCE ("METABOLIC CLEARANCE") OF PLASMA I^{131} (CURVE A), SERUM ALBUMIN CONCENTRATION (CURVE B), AND QUANTITY OF ALBUMIN DEGRADED DAILY (CURVE C)

Following thyroid hormone therapy, there was an appreciable increment in the quantity of albumin degraded even though the concentration of serum albumin decreased.

sized during thyroid administration was obtained from the difference between the total amount degraded and the change in total exchangeable albumin during this period. During the control period the amount synthesized was taken to equal the amount degraded.

RESULTS

Clinical observations and laboratory data which are not related to albumin metabolism are given in the Appendix. It is only necessary to note here that all subjects developed clinical evidence of hypermetabolism akin to that observed in hyperthyroidism within about 2 weeks following initiation of thyroid therapy.

Data pertaining to albumin metabolism are summarized in Table I. During thyroid administration all subjects showed a fall in total serum protein concentration, the mean value decreasing from 7.03 ± 0.20 grams per 100 ml. to 6.26 ± 0.37 grams per 100 ml. Serum albumin concentration fell from 4.62 ± 0.31 grams per 100 ml. to 4.19 ± 0.29 grams per 100 ml. Plasma volume increased in all subjects with a mean change of + 10.4 per cent.

An increase in the overall apparent space of distribution accompanied by a proportionately greater fall in serum albumin concentration resulted in a decrease in TEA of 17 gm. During the control period intravascular albumin was 145 gm. and extravascular albumin 205 gm. After thyroid therapy the values were 143 and 189 gm., respectively, indicating that the slight loss of exchangeable albumin was derived exclusively from the extravascular compartment.

During thyroid administration there was an increased metabolic degradation of albumin in all subjects. This was suggested in the increased urinary excretion of I^{131} (Figure 1, Curves B, D). Although the serum albumin concentration fell, the marked increase in the fractional rate of albumin I^{131} degradation more than compensated for this fall, leading to an increase in the quantity of albumin degraded. Determination of the "metabolic clearance" of albumin I^{131} (Figure 2 and Table I) confirmed the increase in the absolute amount of albumin undergoing metabolic degradation. The mean value of this increase was 81 grams with a range of 32 grams to 165 grams (Table I). Since loss of total exchangeable albumin averaged 17 grams during the same period, the average amount of extra albumin synthesized

during thyroid hormone therapy was 64 grams. Augmented albumin synthesis thus amounted to about 79 per cent of the increase in albumin degradation. In individual subjects the increase in albumin synthesized during thyroid treatment periods of 12 to 22 days ranged from 22 to 128 grams.

DISCUSSION

Previous observations in treated myxedema have established alterations in serum protein concentration and distribution. Thompson, Thompson, Silveus, and Dailey (8) noted a decrease in serum protein concentration when thyroid hormone was administered to two subjects with myxedema, and Boothby, Sandiford, Sandiford, and Slosse (9) observed a negative nitrogen balance following thyroxine administration in myxedema and concluded that extravascular sites were the source of the lost protein. Thompson (10) observed a decrease in blood volume in myxedema which returned to normal with replacement therapy, and Gibson and Harris (11) noted an increased blood volume in hyperthyroid subjects. Schwartz (12) and Lewallen, Rall, Berman, and Hamel (13), employing I^{131} labeled albumin, observed a decrease in extravascular albumin in myxedematous subjects treated with desiccated thyroid. The present study is consistent with these observations and indicates further that the reversal of the abnormalities present in myxedema is not simply referable to correction of a metabolic defect due to lack of thyroid hormone but also that similar changes can be induced by excessive amounts of the hormone even in the absence of such a defect. This is in accord with the widely held concept that thyroid hormone does not produce any qualitative changes in metabolism but acts as a regulator for the quantitative control of autonomous functions. However, the present studies do not rule out the possibility that the changes induced in myxedematous patients and in euthyroid subjects are mediated through qualitatively different mechanisms. Since the precise mechanism of action of thyroid substances has not been definitely established, speculation on this point seems unwarranted at present.

Of special interest is the observation that, under the influence of thyroid hormone, albumin production by the liver increased to a level which nearly compensated for the increased albumin utilization, as a result of which no appreciable negative albumin balance occurred. This is in contrast to previous observations in proteinuric subjects that a decrease in the rate of albumin degradation rather than an increase in the rate of albumin synthesis was the mechanism by which the body generally compensated for the renal losses (2). It was not clear whether the failure to increase the rate of albumin synthesis in these cases represented a pathologic or physiologic limitation, since a protein synthesizing defect in nephrotic proteinuria has previously been suggested (4). However, it has recently been demonstrated that the low serum protein bound iodine levels frequently observed in nephrosis are associated with a diminished rate of metabolism of thyroxin (14). It would then seem that the diminished degradation and limited synthesis of albumin in proteinuria are compatible with normal liver function in a hypometabolic state. The maintenance of a low serum albumin concentration in the presence of significant proteinuria actually minimizes protein loss in the urine and consequent depletion of tissue proteins since albumin excretion would be expected to increase with increased albumin concentration, even if there were no rise in the rate of plasma albumin clearance by the kidneys. Thus, a decrease in albumin degradation without stimulation of albumin synthesis appears to be an economical means of conserving body protein in the presence of proteinuria. Because of the direct stimulation of catabolism, a similar mechanism is not possible in thyrotoxicosis. Hence, the body adapts to protein deficit in different ways depending upon the manner in which this deficit is acquired.

The present study indicates that, at least under the influence of excess thyroid hormone, the normal liver is able to elaborate increased amounts of serum albumin. Whether or not the normal liver can increase its output under euthyroid conditions, assuming the demand is created by increased loss or utilization, cannot be answered by these data. Whipple and Madden (15) observed a rapid restitution of serum protein concentration following plasmaphoresis in dogs and attributed this to an increased rate of protein synthesis. However since the rate of protein degradation was not studied, the possibility that replenishment of protein

stores was effected by significant slowing of protein catabolism rather than by acceleration of synthesis cannot be excluded.

SUMMARY AND CONCLUSIONS

1. Methods are described for the quantitative evaluation of albumin degradation and albumin synthesis under non steady state conditions.

2. The distribution and metabolism of albumin-I^{131} were studied in nine subjects before and after the administration of large doses of desiccated thyroid. Clinical and laboratory evidence of hypermetabolism developed during thyroid administration in all subjects.

3. There was a decline in total serum protein concentration in all subjects with a fall in both albumin and globulin fractions. The total intravascular albumin remained essentially unchanged due to a concomitant increase in plasma volume.

4. The fractional rate and absolute amount of albumin degraded daily increased in all subjects. However augmented albumin synthesis resulted in only a small loss of total exchangeable albumin. This loss was sustained almost entirely by extravascular sites.

APPENDIX

Incidental observations

Since there is a paucity of data on experimental hyperthyroidism in human subjects, the following observations are recorded. In all subjects the first symptoms of hyperthyroidism appeared in about two weeks. Tremor was noted in 7 subjects and heat intolerance in 4. Appetite was noticeably increased in 3 subjects but diminished in 1 patient. None of the subjects developed diarrhea, and only 1 subject noticed an increase in bowel movements. Five of the 9 subjects complained of occipital headache present on arising and lasting for several hours, which is not commonly reported in association with hyperthyroidism. This symptom could not be attributed to hypoglycemia since fasting blood sugar values were normal and the headaches were not relieved by food. There were weight losses of 8 to 19 pounds over the 13 to 25-day periods of thyroid administration in all of the 5 subjects in whom weights were recorded. Blood pressure values remained essentially unaltered during thyroid therapy. The resting heart rate increased to 96 beats per minute or more in 8 of 9 subjects. The basal metabolic rate increased from + 22 per cent to + 49 per cent above the control level with a mean rise of + 37 per cent. In three subjects in whom serum protein bound iodine concentrations were obtained, values ranged from 9 micrograms per cent to 14 micrograms per cent during the period of thyroid administration. Control values were not obtained but the normal range in this laboratory is 3.8 to 7.5 micrograms per cent. Total serum cholesterol concentrations were depressed to approximately 60 per cent of the control values, and no abnormalities in serum bilirubin or cephalin flocculation were noted in 3 subjects. However, in these 3 subjects the thymol turbidity fell from 3.2, 3.4, 1.6 to 1.1, 2.0, 0.5 Shank-Hoagland units, respectively.

ACKNOWLEDGMENTS

We wish to thank Mrs. Katharina Newerly, Biochemist of the Radioisotope Service, for the specially prepared iodoalbumin used in this study. Thanks are also due Mr. Manuel Villazon for technical assistance, Mrs. Melanie Knopf of the Medical Illustration Department for the illustrations and Mrs. Frieda Steiner and Miss Eve Spelke for secretarial assistance.

REFERENCES

1. Berson, S. A., Yalow, R. S., Schreiber, S. S., and Post, J., Tracer experiments with I^{131} labeled human serum albumin: Distribution and degradation studies. J. Clin. Invest., 1953, 32, 746.
2. Bauman, A., Rothschild, M. A., Yalow, R. S., and Berson, S. A., Distribution and metabolism of I^{131} labeled human serum albumin in congestive heart failure with and without proteinuria. J. Clin. Invest., 1955, 34, 1359.
3. Rothschild, M. A., Bauman, A., Yalow, R. S., and Berson, S. A., Tissue distribution of I^{131} labeled human serum albumin following intravenous administration. J. Clin. Invest., 1955, 34, 1354.
4. Addis, T., Glomerular Nephritis, Diagnosis and Treatment. New York, Macmillan Co., 1948.
5. Yalow, R. S., and Berson, S. A., The effect of irradiation damage of albumin-I^{131} on the rate of its *in vivo* metabolism with special reference to the validity of biologic studies with I^{131} labeled proteins. J. Clin. Invest., 1956, 35, 746.
6. Kingsley, G. R., A rapid method for the separation of serum albumin and globulin. J. Biol. Chem., 1940, 133, 731.
7. Berson, S. A., and Yalow, R. S., Quantitative aspects of iodine metabolism. The exchangeable organic iodine pool, and the rates of thyroidal secretion, peripheral degradation and fecal excretion of endogenously synthesized organically bound iodine. J. Clin. Invest., 1954, 33, 1533.
8. Thompson, W. O., Thompson, P. K., Silveus, E., and Dailey, M. E., The cerebrospinal fluid in myxedema. Arch. Int. Med., 1929, 44, 368.
9. Boothby, W. N., Sandiford, I., Sandiford, K., and Slosse, J., The effect of thyroid on the respiratory and nitrogenous metabolism of normal and myxedematous subjects. I. A method of studying the

reserve or deposit protein with a preliminary report of the results obtained. Tr. A. Am. Physicians, 1925, **40**, 195.

10. Thompson, W. O., Studies in blood volume. I. The blood volume in myxedema, with a comparison of plasma volume changes in myxedema and cardiac edema. J. Clin. Invest., 1926, **2**, 477.
11. Gibson, J. G., 2d, and Harris, A. W., Clinical studies of the blood volume. V. Hyperthyroidism and myxedema. J. Clin. Invest., 1939, **18**, 59.
12. Schwartz, E., The effect of thyroid hormone upon the degradation rate and miscible pool of radioiodinated human serum albumin in myxedema. J. Lab. & Clin. Med., 1955, **45**, 340.
13. Lewallen, C. G., Rall, J. E., Berman, M., and Hamel, H., The effects of thyroid hormone on the distribution kinetics and degradation of iodo-albumin. J. Clin. Invest., 1955, **34**, 949.
14. Rasmussen, H., Thyroxine metabolism in the nephrotic syndrome. J. Clin. Invest., 1956, **35**, 792.
15. Whipple, G. H., and Madden, S. C., Hemoglobin, plasma protein and cell protein—their interchange and construction in emergencies. Medicine, 1944, **23**, 215.