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Research Article

THE RELATION OF ALBUMIN TO PRECIPITABLE IODINE OF SERUM [1]

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By correlation with clinical manifestations of thyroid disease, by comparison with basal metabolism, and serum lipids, and by studies of the effects of removal of the thyroid and the administration of thyroid substance and thyroxine, it has been established that the precipitable iodine of the blood serum is, under usual circumstances, a most accurate measure of the activity of the thyroid gland (1 to 6). There is, indeed, reason to believe that the precipitable iodine may be largely, if not chiefly, composed of thyroid hormone. Thyroxine, added to normal serum, attaches itself so firmly to the proteins that it cannot be detached by washing (2). There is some evidence that the fraction of protein with which the iodine is combined is albumin (1). If this is established, this fraction may be regarded as the normal vehicle for the thyroid hormone.

In the serum of certain patients with extreme hypoalbuminemia concentrations of precipitable iodine as low as those found in myxedema have been encountered. The present paper deals with an examination of the incidence and significance of this serum iodine deficiency.

METHODS

From venous blood, drawn from patients in the postabsorptive state, serum was separated with anaerobic precautions. Proteins and fractions were measured by the method of Howe (7) up to January 27, 1947, after which Milne's (8) modification of the procedure, according to the principles of Majoor (9) was employed. This modification yields values which are lower for albumin and higher for globulin than those given by the original Howe technique, agreeing closely with the results of electrophoretic analyses. Serum lipids were measured by the methods of Man, Gildea, Peters and Bogdanovitch (10 to 14). Serum precipitable iodine was measured by the methods of Man and Riggs (2).

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RESULTS

The observations about which the discussion will center are presented in Table I. The coincidence of low serum iodine with extreme hypoalbuminemia was first noted in patient 576, suffering from chronic pyelonephritis with profuse albuminuria as well as biliary cirrhosis. This case will be discussed at greater length below. It was next encountered in two patients with the nephrotic syndrome, B74160 and B95522. Subsequently it was demonstrated in a series of patients with miscellaneous conditions in which hypoalbuminemia appeared to be the only common factor. In a certain number of these patients the effects of thyroid therapy and of injections of salt-poor human albumin upon serum iodine were studied.

DISCUSSION

A review of all patients who have had simultaneous determinations of iodine and albumin reveals no direct correlation between these two variables. This is evident from Figure 1. There is, to be sure, a large aggregation of points in the lower left-hand corner in which both iodine and albumin are reduced together, but these represent multiple observations on the group of subjects now under consideration. Patients with myxedema and minimal quantities of precipitable iodine in their sera may have normal or high concentrations of serum albumin. The correlation between the precipitable iodine of serum and the state of thyroid activity in patients with hyper- and hypothyroidism has been demonstrated at length in previous publications (2 to 6). Although serum proteins were not measured in the majority of these patients, there is no evidence, when it was, that the precipitable iodine was modified by the concentration of serum albumin.

Epstein (15, 16) in 1917 suggested that patients with the nephrotic syndrome had thyroid defi-

TABLE I

Serum precipitable iodine in patients with hypoalbuminemia

Sex	Age	Date	Pptble. I	Protein	Albumin	Globulin	Cholesterol		Fatty acid	Lipid P	Basal metab.	Diagnosis and remarks
							Total	Free				
			γ *per cent*	*per cent*	*per cent*	*per cent*	*mg. per cent*	*mg. per cent*	*mEq. per liter*	*mg. per cent*	*per cent*	
B74160		*1946*										*Nephrotic syndrome*
F	17	11/14	1.5	3.53	1.20	2.33	—	—	—	—	—	
		12/4	0.7	3.79	1.21	2.58	—	—	—	—	—	After thyroid gr. 3 daily for 11 days
		12/16	—	3.93	1.17	2.76	—	—	—	—	—	After thyroid gr. 3 daily for 23 days
		12/24	1.4	—	—	—	631	183	60.5	24.1	—	After thyroid gr. 3 daily for 31 days
		1947										
		1/15	—	3.85	1.20	2.65	—	—	—	—	—	After thyroid gr. 4 daily for 14 days
		2/10	—	3.85	0.75	3.10	—	—	—	—	—	After thyroid gr. 4 daily for 40 days
		2/24	1.0	—	—	—	627	180	60.0	22.1	—	Thyroid gr. 4 daily stopped after 2/19
		3/3	—	4.07	0.62	3.45	—	—	—	—	—	Just before albumin injections
		3/7	—	5.02	1.76	3.26	—	—	—	—	—	After 125 gm. albumin
		3/10	2.0	5.47	2.38	3.09	596	—	51.4	19.9	—	After 275 gm. albumin
		3/15	3.8	5.23	2.13	3.10	471	—	39.7	19.6	—	After 525 gm. albumin
		3/20	—	4.27	0.80	3.47	—	—	—	—	—	
		3/27	3.2	4.08	0.84	3.24	583	168	44.8	21.5	—	
		4/3	2.6	4.66	0.98	3.68	388	—	25.0	—	—	
		4/14	1.7	3.98	0.84	3.14	553	147	41.9	23.2	—	
		7/3	2.3	4.86	0.85	4.01	—	—	—	—	—	
		7/14	2.4	5.27	2.36	2.91	445	—	28.5	—	—	After 475 gm. albumin
B95522		*1947*										*Nephrotic syndrome*
M	32	4/8	2.8	3.27	1.51	1.76	468	147	26.5	20.5	—	
		4/20	—	4.75	2.30	2.45	—	—	—	—	—	After 325 gm. albumin
		4/27	2.9	4.91	3.39	1.52	267	97	21.3	17.2	—	After 675 gm. albumin
		5/5	3.2	4.13	2.22	1.91	255	88	19.7	16.2	—	
		5/23	2.8	—	—	—	323	95	23.8	18.0	—	After thyroid gr. 2 daily for 14 days
		6/11	1.9	3.79	1.52	2.27	260	95	21.4	19.6	—	After thyroid gr. 4 daily for 14 days
		7/11	2.1	3.93	1.11	2.82	—	—	—	—	—	
		7/29	—	3.05	0.76	2.29	—	—	—	—	—	
		7/30	0.7	—	—	—	—	—	42.7	25.9	—	On thyroid gr. 2 daily
		8/15	0.3	3.63	1.53	2.10	594	153	31.0	—	—	After 500 gm. albumin
B72419		*1947*										*Intercapillary glomerularsclerosis. Diabetes*
M	28	6/12	—	3.96	1.16	2.80	—	—	—	—	—	
		6/16	4.4	—	—	—	367	99	20.7	13.8	—	
		6/23	—	6.02	3.01	3.01	—	—	—	—	—	After 300 gm. albumin
		6/24	1.8	—	—	—	316	84	24.9	—	—	
576		*1945*										*Chronic pyelonephritis. Biliary cirrhosis. Myxedema ?*
F	64	4/16	—	3.24	1.15	2.09	—	—	—	—	—	
		4/20	1.3	—	—	—	562	—	32.7	—	—	
		4/26	—	3.10	1.10	2.00	—	—	—	—	−12	
		5/8	—	5.91	1.00	4.91	—	—	—	—	—	
		5/9	1.3	—	—	—	589	206	65.0	21.7	—	After thyroid gr. 1 daily for 11 days
		6/6	3.4	—	—	—	552	176	33.4	18.4	—	After thyroid gr. 3 daily for 18 days
		9/5	—	3.34	1.38	1.96	365	130	23.4	12.5	—	After thyroid gr. 4 daily for 2½ mos.
		10/26	5.0	4.27	1.85	2.42	352	120	28.3	15.1	—	Still taking thyroid gr. 4 daily
		1946										
		5/1	5.1	3.63	1.50	2.13	201	73	12.8	8.8	—	Still taking thyroid gr. 4 daily
		5/21	5.0	3.90	1.58	2.32	—	—	—	—	—	On thyroid gr. 3 daily since 5/8
		6/3	2.8	4.11	2.21	1.90	—	—	—	—	—	Still taking thyroid gr. 3 daily
B44829		*1947*										*Diabetes. Cirrhosis of liver, probably biliary*
F	75	7/31	—	—	—	—	170	65	15.6	9.5	—	
		8/15	—	5.73	1.93	3.80	—	—	—	—	—	
		8/21	—	6.17	3.44	2.73	—	—	—	—	—	After 275 gm. albumin
		8/28	—	6.52	3.98	2.54	61	31	7.3	5.2	—	After 275 gm. albumin
B96023		*1947*										*Cirrhosis of the liver*
M	59	4/17	4.2	7.17	1.33	5.84	163	81	13.2	11.2	—	

TABLE I—*Continued*

Sex	Age	Date	Pptble. I	Protein	Albumin	Globulin	Cholesterol		Fatty acid	Lipid P	Basal metab.	Diagnosis and remarks
							Total	Free				
			γ *per cent*	*per cent*	*per cent*	*per cent*	*mg. per cent*	*mg. per cent*	*mEq. per liter*	*mg. per cent*	*per cent*	
B78803		*1946*										*Cirrhosis of the liver*
M	62	4/10	—	5.89	2.66	3.23	129	47	9.3	8.2	—	
		5/16	—	6.10	3.20	2.90	92	41	9.4	7.7	—	After 462 gm. albumin
B82147		*1947*										*Calcified pericardium*
M	33	6/16	3.0	4.20	1.61	2.59	141	43	11.0	—	—	
		7/7	1.9	3.97	2.66	1.31	79	25	7.6	—	—	After 800 gm. albumin
B97275		*1947*										*Vomiting and diarrhea, unexplained. Nutritional edema*
F	63	6/4	5.2	3.02	1.37	1.60	115	42	9.2	—	—	
		6/17	3.8	4.23	2.66	1.57	—	—	—	—	—	After 475 gm. albumin
12377		*1947*										*Exfoliative dermatitis*
F	44	3/17	3.7	4.56	0.93	3.63	58	20	5.2	6.1	—	
A76963		*1947*										*Thrombophlebitis. Nephrotic syndrome*
M	45	9/22	—	5.33	1.26	4.07	—	—	—	—	—	
		9/24	3.0	—	—	—	—	—	—	—	—	
		9/29	—	5.76	1.21	4.55	—	—	—	—	—	
		10/2	—	5.69	1.23	4.46	—	—	—	—	—	
		10/6	7.0*	—	—	—	241	69	11.3	10.7	—	After 175 gm. albumin
		10/8	—	5.79	1.50	4.29	—	—	—	—	—	After 275 gm. albumin
		10/14	—	6.23	2.97	3.26	—	—	—	—	−13	After 525 gm. albumin
		10/21	3.5	—	—	—	268	78	12.8	10.9	—	4 days after 575 gm. albumin
71570		*1947*										*Craniopharyngeoma. Pituitary deficiency?*
M	59	7/22	2.6	4.95	2.10	2.85	108	25	6.4	6.3	—	
		9/9	2.0	5.19	1.79	3.40	—	—	—	—	—	After thyroid gr. 2 daily for 14 days
A86708		*1942*										*Anorexia nervosa*
		6/3	5.6†	6.82	—	—	—	—	—	—	−22	
P3027		*1943*										*Anorexia nervosa*
		1/8	3.7†	4.96	3.83	1.13	199	64	10.9	9.1	−33	
		2/11	3.6†	5.68	3.72	1.96	176	—	9.6	—	−25	
		10/23	4.8†	6.07	—	—	—	—	—	—	−25	
B10436		*1944*										*Anorexia nervosa*
		1/28	5.6	5.59	4.32	1.27	129	41	11.5	7.5	—	
B71694		*1945*										*Anorexia nervosa*
		8/23	4.7	6.73	4.09	2.64	—	—	—	—	−28	
B6589		*1945*										*Anorexia nervosa*
		8/10	—	6.16	4.42	1.74	—	—	—	—	—	
		8/21	5.4	—	—	—	—	—	—	—	—	
B77426		*1946*										*Anorexia nervosa?*
		4/4	3.1	7.00	5.14	1.86	—	—	—	—	−24	
B74923		*1946*										*Hypopituitarism*
M	29	2/7	3.3	—	—	—	—	—	—	—	—	
		2/12	—	—	—	—	—	—	—	—	−31	
		3/27	3.6	6.72	4.49	2.23	206	66	29.8	12.0	—	
		5/3	6.7	—	—	—	—	—	—	—	—	On thyroid gr. 1 daily
		6/1	—	—	—	—	—	—	—	—	−22	On thyroid gr. 1 daily
		1947										
		8/6	1.7	—	—	—	—	—	—	—	+29	On thyroid gr. 1 daily

TABLE I—*Continued*

Sex	Age	Date	Pptble. I	Protein	Albumin	Globulin	Cholesterol		Fatty acid	Lipid P	Basal metab.	Diagnosis and remarks
							Total	Free				
			γ per cent	*per cent*	*per cent*	*per cent*	*mg. per cent*	*mg. per cent*	*mEq. per liter*	*mg. per cent*	*per cent*	
B76181		*1946*										*Hypopituitarism*
M	16	1/21	—	6.70	—	—	—	—	—	—	—	
		1/26	3.4	—	—	—	—	—	—	—	—	
		3/21	2.9	—	—	—	229	—	10.9	—	—	
		1947										
		1/13	3.2	—	—	—	146	—	7.9	—	−19	On thyroid gr. 3 daily
		8/4	3.9	—	—	—	—	—	—	—	—	On thyroid gr. 4 daily
		8/21	—	6.39	3.62	2.77	—	—	—	—	—	
		10/31	1.3	—	—	—	—	—	—	—	—	On thyroid gr. 4 daily
B69216		*1945*										*Hypopituitarism*
M	44	5/25	1.7	—	—	—	—	—	—	—	−29	
		5/31	—	—	—	—	247	—	12.3	9.3	—	
		6/18	4.7	—	—	—	—	—	—	—	−33	On thyroid gr. 2 daily
		11/22	2.2	—	—	—	—	—	—	—	—	On thyroid gr. 2 daily
B98193		*1947*										*Hypopituitarism*
M	47	9/19	2.9	—	—	—	—	—	—	—	—	
		10/4	—	6.28	3.77	2.51	281	80	16.4	11.7	—	
		10/14	5.1	—	—	—	—	—	—	—	—	

* This sporadic high figure is quite inexplicable. † Figures for total serum iodine instead of precipitable iodine.

ciency and were benefitted by administration of thyroid substance. He based this opinion upon the low basal metabolism and high serum cholesterol that commonly occur in this condition. These chemical disorders are not, however, associated with the clinical symptoms or signs of hypothyroidism. Furthermore, it has been pointed out that the lipemia of the nephrotic syndrome differs from that of myxedema. In the former, neutral fat is increased, as well as cholesterol and phospholipids, while in myxedema the increment of fatty acid appears to be derived entirely from cholesterol esters and phospholipids (17). These features are well illustrated by B74160 of this series (B95522 is not so characteristic because his nephrosis was complicated by thrombophlebitis and liver disease). The patient B74160 was a vivacious girl of 18, mentally alert and physically rather hyperactive, with a variable, but persistent, tachycardia. Her skin and hair were normal in texture, her vasomotor reactions somewhat excessive. Presumably her basal metabolism was low. Her serum lipids were greatly elevated, with more than the usual proportion of fatty acids. The administration of dried thyroid (U.S.P.), in doses as great as 4 grains per day over long periods, had no appreciable effect upon the lipids of her serum nor did it cause the serum precipitable iodine to rise appreciably. It was impossible to determine whether it influenced her heart rate because as was remarked above, she had a variable, but persistent, tachycardia at all times. The tachycardia while she was taking 4 grains of thyroid daily was no greater than it was at some other times when she was receiving no thyroid. The thyroid had no detectable effect upon her weight or edema. This in itself distinguishes her from the true hypothyroid patient who reacts sharply and quantitatively to smaller doses of thyroid (3, 5). Patient B95522 reacted, or failed to react, in a similar manner to an equally large dose of thyroid. His serum lipids were not, however, as distinctly elevated as those of B74160. The ratio of free to total cholesterol in his serum was slightly above normal, and the proportion of fatty acid was not excessive. These modifications of the usual nephrotic pattern were probably referable to the hepatic disorder.

It seemed possible that the low serum iodine represented not a diminution in the production of thyroid hormone or the amount available to the tissues, but merely a deficiency of the vehicle, serum albumin, by which it is carried in the blood stream. The reaction to the injection of salt-poor

human serum albumin was, therefore, examined.[2] This albumin itself contained minimal amounts of iodine. Analysis yielded 3.0 to 4.6 γ per 100 cc., containing 25 gm. of albumin. If the precipitable iodine of serum is held entirely by the albumin fraction of the proteins, 25 gm. of normal serum albumin should contain from 24 to 48 γ. The first time that albumin was administered to B74160 her serum iodine seemed to rise slightly, from 1.0 to 3.8 γ per cent; but on subsequent occasions in this subject and on almost all occasions in other subjects no such response was observed. In fact, in most instances the serum iodine tended to fall.

Patients with nephrosis do not constitute the most suitable subjects for the examination of the effects of injections of serum albumin because the material is so rapidly excreted in the urine that its effect on the concentration of albumin in the serum is quite evanescent. By daily injections of the albumin it was, however, possible to maintain the serum albumin of B74160 for a week about 1.5 per cent above its initial value. This should have been long enough to allow some kind of new equilibrium to be established.

In the nephrotic syndrome excretion in the urine of iodine combined with protein might contribute to the serum iodine deficiency. Measurement of the iodine attached to urinary protein proved to be a difficult technical problem because it required the treatment of such large volumes of material. A 24-hour sample of urine from B74160 contained 11.70 gm. of protein which, in turn, held 16.05 γ of iodine, or 1.37 γ of iodine per gram of protein. The serum, by the Howe technique, contained 3.9 and 1.2 per cent of total protein and albumin, respectively, and 1.4 γ per cent of pre-

[2] The serum albumin used in the research described herein was furnished by the Administrator of the National Blood Program, American Red Cross, on recommendation of the Subcommittee on Blood and Blood Derivatives of the Red Cross Medical Advisory Committee.

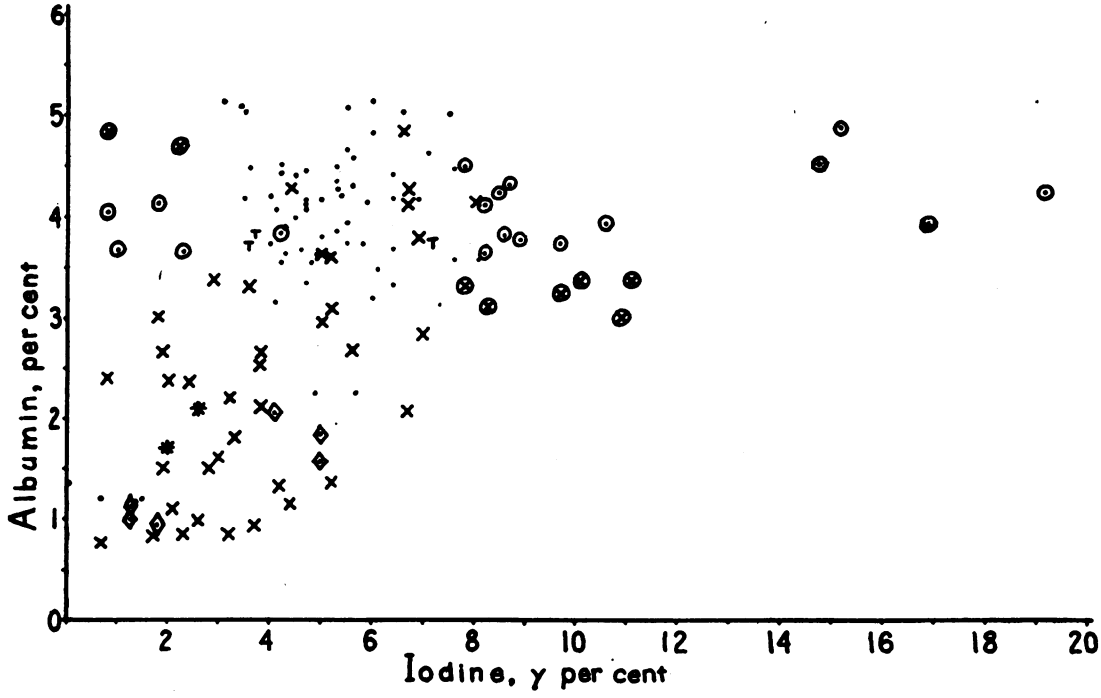

FIG. 1. THE RELATION OF PRECIPITABLE IODINE TO ALBUMIN OF SERUM

•—Albumin by Howe method.
×—Albumin by Milne-Majoor method.
T—Albumin by Howe method, total serum iodine.
Open circles about dots and crosses represent patients with myxedema and hyperthyroidism.
Diamonds mark determinations upon patient No. 576, discussed in the text.
Stars mark the determinations on patient No. 71570, also discussed in the text.

cipitable iodine. The serum therefore contained $1.4/3.9 = 0.36\,\gamma$ of iodine per gram of protein or $1.17\,\gamma$ of iodine per gram of albumin. The urine of 576 on one occasion contained 1.7 to $3.0\,\gamma$ of iodine per gram of protein, while the serum contained $0.52\,\gamma$ per gram of total protein or $2.0\,\gamma$ per gram of albumin. Without more precise knowledge of the partition of protein fractions in serum and urine, respectively, the proportions of iodine to protein in the two media cannot be accurately compared. If all the protein in the urine was albumin, which can hardly have been the case, and all the iodine in the serum was bound by albumin, urine albumin and serum albumin held approximately the same amounts of iodine. Compared on the basis of total protein in the two media, more iodine was held by the urine protein than by the serum protein in both instances. This might be anticipated from the known differences between the electrophoretic patterns of serum and urine in the nephrotic syndrome (18). The actual quantities of iodine lost in 24 hours, from 16 to $48\,\gamma$, are far smaller than the hormonal requirements of normal individuals estimated from the amounts of thyroid substance or thyroxine needed to maintain a patient with myxedema in a euthyroid state. Although losses of iodine with protein in the urine may, in nephrosis, contribute to the depletion of serum precipitable iodine, they cannot be wholly accountable for it. Moreover, they can not account in any degree for the serum iodine deficiency in cirrhosis of the liver and the other conditions in which it is found in association with hypoalbuminemia in the absence of proteinuria.

From Figure 1 precipitable iodine appears to be affected by serum albumin only when the latter is profoundly reduced. The clinical material from which this figure is composed is, however, so variable that it could not be asserted with any assurance that lesser variations of serum albumin have no influence upon serum iodine. It is conceivable that the serum iodine deficiency is connected not only with the degree, but also with the nature, of the albumin deficit. It has been shown that in the hypoalbuminemia of the nephrotic syndrome and of cirrhosis of the liver the two chief fractions of serum albumin do not suffer equal depletion. It might be anticipated that if only one fraction, the vehicle of iodine, was depleted, injection of whole serum albumin would restore the vehicular capacity of the serum. The major proportion of the injected albumin does not, however, remain in the circulation. The salt-poor human albumin employed for these injections contains far less iodine than normal circulating albumin is believed to carry. It has, in fact, been suggested that iodine is carried not by albumin but by α-globulin. In this case injection of albumin could not increase, but should rather tend to diminish its concentration in serum. On the other hand, this would make the deficiency of serum precipitable iodine in hypoalbuminemia the more inexplicable, since α-globulin usually increases when albumin diminishes.

When the serum albumin of the nephrotic subjects rose under the influence of injections of albumin, the lipids fell without any disturbance of the relative proportions of the various fractions. Barker and Kirk (19) in 1930 reported that serum protein and cholesterol varied inversely in dogs subjected to plasmapheresis. This was not confirmed by Leiter (20). That there is no consistent inverse relation between these variables in disease in general has been amply demonstrated. In malnutritional states with hypoalbuminemia the serum lipids are usually reduced (21). This is true also in hepatic cirrhosis and advanced degeneration of the liver (22). Both also fall together after operations (23). In renal hyperlipemia itself there is no consistent inverse correlation between the albumin and lipids of the serum. It is clear from Table I that in all these conditions injections of albumin had a similar effect: the serum lipids fell, whether they were initially high or low. The reductions thus induced cannot be interpreted as evidence of improvement in nephrosis since it occurred equally in all patients, including those with cirrhosis of the liver and hypolipemia, whether there was a concomitant diuresis or not. These reductions must be attributed not to any action that albumin may exert upon the underlying disease, but rather to some more specific action upon the chemical structure of the serum. They cannot be ascribed simply to hemodilution because they are altogether too great in many instances and are not proportional to the decreases of other elements such as globulin. Furthermore, they appear to outlast the other effects of albumin.

The majority of these patients are malnourished —*i.e.*, they are suffering from protein deficiency. This state is regularly accompanied by a reduction of basal metabolism (23 to 25). It has been tacitly assumed by some that oxidation is retarded by inhibition of pituitary activity when the supply of food becomes inadequate. The reduction of basal metabolism, according to this theory, arises from absence of thyrotrophic hormone. The striking similarity between the symptoms and signs of anorexia nervosa and those of Simmond's disease lends plausibility to this view (26). It might be inferred that both the reduction of basal metabolism and the serum iodine deficit of hypoalbuminemia are evidences of thyrotrophic inhibition in response to protein deficiency. If this were the case, similar phenomena should be observed in anorexia nervosa. In this peculiar state, however, the concentration of serum albumin is relatively well preserved. This is illustrated by the six cases presented in Table I. It will also be noted that serum precipitable iodine may remain within normal limits, although the basal metabolism is reduced to levels comparable to those seen in patients with myxedema. In only one of the six cases, B77426, is serum iodine definitely below normal limits. There is reason to question the diagnosis in this case on entirely independent grounds. The figures in P3027 are probably also below normal if consideration is given to the fact that they must be corrected for free iodine. The fact remains, however, that extreme malnutrition of anorexia nervosa with striking hypometabolism may be associated with normal serum albumin and serum precipitable iodine.

The discovery that hypoalbuminemia may be associated with serum iodine deficiency in the absence of definite evidence of hypothyroidism is a distinct challenge to the diagnostic value of the precipitable iodine method. Patients with low serum albumin have always presented a diagnostic problem. The basal metabolism, on which reliance has been generally placed, is of doubtful value in this state; serum cholesterol is equally unreliable. Reasons have been given for discounting these methods in the nephrotic syndrome. It cannot be assumed that the serum iodine deficiency is a sign of inactivation of the thyroid in response to malnutrition in view of the findings in anorexia nervosa. Indeed, the failure of serum albumin to fall consistently in this disorder is one of a number of disturbing facts that may compel revision of the widely accepted theory that depletion of protein *per se* gives rise to hypoalbuminemia. The concentrations of precipitable iodine and of albumin in the sera of patients with authentic anterior pituitary deficiency have not been extensively investigated, as far as the authors are aware. Our own scanty data on the subject are presented in Table I. In one patient, B74923, with a chromophobe adenoma of the anterior pituitary with hypogonadism and extremely low urinary 17-ketosteroids, when the basal metabolism was -31 per cent the serum iodine was 3.6 γ per cent, serum albumin 4.49 per cent (Howe) and total cholesterol 206 mg. per cent. There was no evidence in serum electrolytes or chloride excretion of adrenal cortical deficiency. A patient, B76181, with a craniopharyngeoma and low urinary 17-ketosteroids, again without evidence of adrenal cortical insufficiency, had a basal metabolism of -28 per cent and serum precipitable iodine varying from 2.9 to 3.9 γ per cent. Serum albumin on one occasion was 3.62 per cent (Milne). Cholesterol fell from 229 to 146 mg. per cent under thyroid therapy, while serum precipitable iodine rose from 2.9 to 3.2 γ per cent. B69216, with a suprasellar tumor and hypogonadism, in addition to disturbances of the metabolism of bicarbonate and chloride indicative of adrenal cortical insufficiency, had a serum precipitable iodine of 1.7 γ per cent and a total cholesterol of 247 mg. per cent. In this case serum proteins were not measured. B98193, with presumably a chromophobe adenoma of the pituitary, had hypogonadism and adrenal cortical insufficiency. His serum albumin and cholesterol were normal, his precipitable iodine on one occasion low, on another within normal limits. If these cases are characteristic, hypopituitarism appears to lower basal metabolism and serum precipitable iodine, but not serum albumin nor cholesterol. The subject requires further investigation; but tentatively the effect of pituitary insufficiency on the composition of serum seems to differ from those of either anorexia nervosa or disorders attended by hypoalbuminemia. Among the features of hypopituitarism that require further inquiry is the apparent tolerance to thyroid developed by patients with these conditions. The iodine of the first three cases responded to thyroid medication

at first; but in each instance fell subsequently, although the dose of thyroid was maintained.

The clinical importance of the phenomenon can be best illustrated by two cases from the present series. The first, 576, Table I, has already been mentioned. The patient, a woman of 64, had profuse albuminuria with some evidences of arteriosclerosis and mild renal insufficiency, hypoalbuminemia of a severe grade, massive edema of the lower extremities and the lower two-thirds of the trunk, ascites and bilateral hydrothorax. A little earlier an operation had revealed a spontaneous cholecystcolostomy and a large gall-stone obstructing the colon. She had some hepatic insufficiency and bronchiectasis. She was extremely malnourished and able to eat little because of anorexia, nausea and occasional vomiting. Because of the dry, shrivelled appearance of her skin, scanty, falling hair and other stigmata suggestive of myxedema, serum precipitable iodine was measured, which proved to be only 1.3 γ per cent. Thyroid was, therefore, prescribed. A dose of 1 grain had no detectable effect. Even after she had received 3 grains daily for almost three weeks, the serum iodine was only 3.4 γ per cent. Finally, on 4 grains daily it rose to 5.0 γ per cent. The patient, however, wasted rapidly. Subsequently, when the dose of thyroid was reduced to 3 grains daily, the precipitable iodine fell to 2.8 γ per cent. It is, of course, impossible to say whether the large dose of thyroid accelerated wasting, in view of the numerous disorders from which she suffered. It was necessary, however, in order to bring her serum iodine into the lower normal range, to give as much thyroid as is usually required to induce hyperthyroidism and excessively high serum iodine in patients with true myxedema. Postmortem examination revealed, in addition to the fistula between the bile duct and the colon, chronic pyelonephritis, biliary cirrhosis and bronchiectasis, a thyroid gland that was somewhat hypoplastic, but had not the characteristic appearance of a myxedematous gland. It may well be that the low serum precipitable iodine was related only to the hypoalbuminemia in this case and that thyroid medication, by accelerating her metabolism, hastened her demise.

The second patient, 71570, a 59 year old male, was admitted to the hospital because of a subdeltoid bursitis and a chronic infection of the left maxillary antrum. In addition he had been losing weight, strength and energy progressively for about four years. X-ray of the skull indicated that he had a craniopharyngeoma. He was wasted and had extreme anorexia. Blood sugar curves and studies of salt metabolism yielded no evidences of adrenal cortical insufficiency. Gonadal hypofunction was hard to evaluate in view of the undernutrition, but urinary 17-ketosteroids were distinctly reduced. His skin had a silky texture. Serum albumin and precipitable iodine were both low. At the same time the lipids were greatly reduced as they are in patients with malnutrition, in contrast to the normal values frequently encountered in pituitary insufficiency. On 2 grains of thyroid daily for two weeks, together with 30 mg. of methyltestosterone, the serum iodine did not rise; if anything, it fell. In this respect he differs sharply from the usual hypopituitary case. At the same time serum albumin diminished and his weight decreased. Again the question must be raised whether the low iodine in this case represented thyroid deficiency or was only associated with the hypoalbuminemia. The latter, in this case, was not so low as it was in the other cases with iodine deficits.

SUMMARY

In patients with profound hypoalbuminemia the precipitable iodine of the serum is often reduced to concentrations as low as those found in myxedema, without clinical evidence of thyroid deficiency. Administration of active thyroid substance in doses that are effective in the treatment of myxedema does not raise the precipitable iodine of these patients. Injections of enough salt-poor human albumin to raise the serum albumin of these patients considerably, does not consistently raise, and more often decreases, the precipitable iodine. The significance and clinical implications of the serum iodine deficiency are discussed.

Injection of enough salt-poor human albumin to raise the serum albumin of patients with hypoalbuminemia considerably causes the serum lipids to fall. This decrease occurs whether the lipids were originally high or low and affects all lipid fractions proportionally.

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