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Variations in Alkali Reserve of Plasma and Excretion of Total Titratable Urinary Acid in Hyperthyroidism.

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The literature on the alkali reserve of the plasma in hyperthyroidism is small and is inconclusive, particularly in view of the scarcity of serial studies[1-8] and the inclusion of complicated cases. Accordingly, we made serial observations on 15 hospitalized patients between 1933 and 1935 and the pertinent findings are given in Table I. Similar observations on 3 patients in a more recent series appear in Table IV. None of these patients had any complicating metabolic disease and one had cardiac decompensation; the occurrence of auricular fibrillation in 3 patients in Table I is noted. All estimations were made in the basal state: blood was taken from the unobstructed vein, usually under oil, into tubes containing neutral potassium oxalate, centrifuged immediately and the CO_2 combining power of the separated plasma was determined, ordinarily at once, by the method of Van Slyke and Cullen.[9] Rarely, the separated plasma was kept in the ice box, but the determination was made within one hour of vena puncture. Postoperative observations were made on the fifth to seventh day. It seemed suggestive that, of the 18 patients, 8 showed a rise of from 3 to 14 vol. % with improvement of the thyroid status and that in the more severe stages of hyperthyroidism values for CO_2 combining power tended toward the lower limits of the normal range. There was, clearly, no direct correlation between the level of basal metabolism alone and the value for CO_2 combining power of the plasma.

In view of these findings further investigation of the acid-base regulatory mechanisms were made by serial determinations of the total titratable acid of the urine.[10] Another series of patients was

1 Davies, H. W., Meakins, J., and Sands, J., *Heart*, 1924, **11**, 299.
2 Walinski, F., and Herzfeld, E., *Muenchen med. Wchnschr.*, 1926, **73**, 2153.
3 Damble, K., and Reuter, A., *f. Klin. Med.*, 1933, **125**, 690.
4 Coelko, E., *Endokrin.*, 1932, **10**, 74.
5 Altenburger, E., and Boger, A., *Klin. Wchnschr.*, 1933, **12**, 1983.
6 Skold, E., *Arch. f. Klin. Chir.*, 1928, **151**, 600.
7 Zondek, H., *Deutsch. med. Wchnschr.*, 1929, **55**, 345.
8 Koenig, W., *Arch. Klin. Chir.*, 1931, **164**, 213.
9 Van Slyke, D., and Cullen, G. E., *J. Biol. Chem.*, 1917, **30**, 289.
10 Folin, O., *Am. J. Physiol.*, 1903, **9**, 25.

hospitalized and kept until operation on diets which were constant in the quantities of basic and acid-forming components and of constant caloric intake. The diets necessarily varied somewhat, one from another, to suit the food preferences and eating habits of the individual patients. A period of 2 or 3 days was allowed to elapse before collection of 24-hour urines in stoppered bottles containing 2 cc of toluene was begun. (Bottles and collecting vessels were sterile in Case 9 in whom organic acid and ammonia nitrogen were also determined.) All estimations were made in duplicate. The diet was resumed on the third or fourth postoperative day.

The data on 9 cases in which this constant regime could be maintained appear in Table II. Characteristic excerpts for consecutive days at 3 intervals during hospitalization, with the mean acidity and the range during such period are presented. (The complete protocol of Case 9 covers 8 weeks.) A consistently close relationship exists between the course of the individual case and the quantity of acid excreted. Where prompt relief of hyperthyroidism occurs shortly after operation, a fall to one-half or one-fourth of the original level is seen; indeed, in Case 3, urine alkaline to phenolphthalein was obtained on two occasions postoperatively. Where the clinical im-

TABLE I.
Basal Metabolic Rate and Carbon Dioxide-Combining Power of Plasma Before and After Thyroidectomy.

	Unstab.		Pre-op.		Post-op.	
Ex. G.	BMR	CO_2 combining power of plasma volume % CO_2	BMR	CO_2 combining power of plasma volume % CO_2	BMR	CO_2 combining power of plasma volume % CO_2
1. 30, M	+91†	50	+32†	60	+ 4	64 d
2. 50, F	+75?	56			+10	56
3. 22, M	+70?	61	+16	60	+11	59 d
4. 39, F	+40	55	+37	53*	+ 7	53
5. 42, F	+80?†	51	+42	52*	+24	59
6. 44, F			+34†	54	+16†	55 d
7. 23, F	+26	58	+14	62	— 4	65 d
8. 29, M	+64	60	+23	61	+19	60 d
9. 37, F			+16	57	+ 5	60 d
Tox. Ad.						
10. 59, F	+32	72	+14	68	+15?	74
11. 38, F			+22	61	—15	57
12. 48, F			+25	62	— 9	67
13. 36, F	+45	57			+ 2	67
14. 27, F			+ 3	61	0	59
15. 52, F			+31	59	+16	58

*Vena puncture difficult.
†Auricular fibrillation.
d. 2-stage thyroidectomy.

TABLE II.
Total Titratable Acid of Urine in Hyperthyroidism.

Case	Unstabilized (admitted)			Pre-op.			Post-op. (discharged)		
	Days	Acid cc 0.1N	BMR	Days	Acid	BMR	Days	Acid	BMR
1. 52, F	4	270 (334-204)	+38	2	93 (136- 50)	+20	3	85 (122- 62)	
2. 44, F				5	237 (299-153)	+18	3	251 (291-209)	+19
3. 48, F	1	180	+38	4	64 (84- 46)	+17	4	18 (51- 0)	+10
4. 29, F	7	316 (422-257)	+41	3	247 (263-233)	+15	3	128 (136-111)	+ 4
5. 56, F	7	276 (326-207)	+29	3	193 (273-153)	+21			
				3	155 (228-111)	+11	4	126 (163- 68)	+ 4
6. 32, F						+38	5	195 (249-142)	+12
							3	92 (90- 94)	
7. 17, F	6	382 (455-294)	+38						
							5	136 (204- 73)	+ 5
8. 60, F	3	314 (348-262)	+36	6	197 (252-100)	+31			
							9 { 5	327 (429-185)	
							9 { 4	220 (238-177)	+19
9. 19, F	5	357 (388-315)	+50	10	135 (193- 86)	+24			
						+16	6	96 (147- 65)	—13

provement over the preoperative status is slight in the early postoperative phase (Cases 2, 8), little or no change in total acid excretion occurs as expressed in averages. In Cases 5, 6, 7, 8, 9 two-stage thyroidectomy was done; preoperative observations on Cases 8 and 9 precede first lobectomy in both instances. All postoperative observations in two-stage cases (except Case 6) are subsequent to the second lobectomy, hence they appear on the line below that on which admission observations are recorded. Physical activity in all cases was limited to getting from bed to a chair and to the bathroom.

Table III presents further excerpts from the protocol of Case 9 and it is seen that in the brief phase in which she is temporarily getting worse (on 1/27 and 1/28) her organic acid excretion[11] and ammonia nitrogen[12] rise, along with the total titratable acid, and that the pH of the urine falls. These associations were quite constant throughout the prolonged period of observation. On the contrary, the opposite trends appear in the findings on her last 4 days before discharge following her second lobectomy at a time when she was improving rapidly.

During this study of acid excretion, we resumed the estimation of

TABLE III.
Constituents of 24-hour Urine Before and After Thyroidectomy. Extracts of Protocol of Case 9.

	Case 9.								
	Pre-op					Post-op.			
Date	1/25	1/26	1/27	1/28		3/6	3/7	3/8	3/9
Vol.	2100	1500	2100	2650		3100	2750	2350	2740
T. acid	142	102	172	190	Op.	99	99	65	65
O. "	26.8	14.4	20.1	33.9	2/7	35.9	26.4	26.3	21.9
NH_3 N	.239	.211	.281	.439	and	.558	.481	.439	.446
pH	6.0	6.0	5.8	5.8	2/29	6.5	6.5		7.0
BMR				+32					—13

Total acid, cc 0.1N per 24 hr.
Organic acid, milli eq. per 24 hr.
Ammonia N, g per 24 hr.

TABLE IV.
CO_2 Combining Power of Plasma and Urinary Acid.

	Unstabilized			Pre-op.			Discharge		
Case	Acid	CO_2*	BMR	Acid	CO_2*	BMR	Acid	CO_2*	BMR
3.	180	59	+38	64	60	+17	18	66	+10
4.	316	56	+41	247		+15	128	60	+ 4
8.	314	60	+36	197	58	+31	220	60	+19

*CO_2 combining power of plasma, vols %.

11 Van Slyke, D., and Palmer, W., *J. Biol. Chem.*, 1920, **41**, 567.
12 Folin, O., and Bell, R., *J. Biol. Chem.*, 1917, **29**, 329.

CO_2 combining power of the plasma in 3 cases and these results appear in Table IV. In Cases 3 and 4, in which prompt improvement of thyroid status occurred, a definite rise in CO_2 combining power accompanied the fall in excretion of total acid; in Case 8, clinical improvement did not occur so soon after operation and no rise in alkali reserve or fall in urinary acid excretion is seen. Further studies are needed to determine the existence of a correlation here.

The tendency of severely thyrotoxic patients to show impaired liver function is firmly established, yet no correlation can be shown between the severity of hyperthyroidism and the extent of functional hepatic deficiency. Somogyi[13] has recently demonstrated important accumulations of ketone bodies in the blood of hyperthyroid patients and while we have not identified the organic acids, the excretion of which is so largely increased in Case 9 (rising above 50 milli-equivalents at one time), we should expect them to be beta-hydroxybutyric and aceto-acetic acids. We assume the increased ammonia nitrogen excretion in this case to be an indication of stress on base economy of the body during the exacerbations of hyperthyroidism.

Summary. Serial observations on 18 patients reveal a rise of carbon dioxide-combining power of the plasma in 8 cases as their clinical status improves with treatment and operation. All values fall within the normal range. The excretion of total titratable acid of the urine in 9 patients on constant diets is reported. In the patients in whom decided improvement occurs shortly after operation, the preoperative amounts are from 2 to 4 times as large as those excreted postoperatively. Excretion of organic acids and ammonia nitrogen were also followed for nearly a month in one patient and in exacerbations of hyperthyroidism her excretion of these substances, as well as of total acid, is seen to rise; urinary pH values fall during exacerbations. In 2 patients who improved promptly following thyroidectomy, fall in total acid excretion is accompanied by a rise of alkali reserve; in a third patient who showed little early improvement and only a slight change of total acid excretion, there was no change in carbon dioxide-combining power of the plasma.

These findings are consistent with the existence of a compensated acidosis in hyperthyroidism.

[13] Somogyi, M., personal communication.