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Effects upon Blood Amylase of Variations in Thyroid Activity.

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The sensitive method of Somogyi for the quantitative determination of blood amylase[1] permits the estimation of very low quantities of the enzyme. This quality of the method has led to the observation that low levels of blood amylase are found as a rule whenever liver functions are impaired.[1] Low amylase values were frequently observed in cases where dysfunction of the liver was of a moderate degree and could not be proved by the customary clinical methods employed for estimating liver function. It is the view of Somogyi and his coworkers, based on a very large experience, that amylase derives largely from the liver, hence the level of amylase in the blood is considered to be an important indication of liver function.

We have had the opportunity of doing occasional estimations of blood amylase since 1934 in the course of other work and the frequent finding of rather low values in patients with thyrotoxicosis, particularly before treatment is instituted, has seemed to warrant an investigation of serial determinations at varying levels of thyroid activity. This has been followed in two directions: 1. as thyroid activity increases with thyroid feeding in hypothyroidism; 2. as thyroid activity in hyperthyroidism is diminished by treatment with iodine and thyroidectomy.

The blood amylase for normal subjects will fall between values of 80 and 150 in about 90% of cases; approximately 5% give values down to 50 and a further 5% range from 150 to 200; the individual values remain remarkably constant for the healthy person. Before the serial study which forms the subject of this report was undertaken, the following isolated observations were made on patients with toxic goiter.

1. Untreated: 1/3/35, M.A.V., 60; 5/24/35, E.B., 30; 5/18/35, B.M., 66.
2. Treated (preoperative): 12/10/34, R.C., 72; A.H., 4/26/35, 108; 4/23/35, M.K., 75; 4/22/35, M.V., 86; 5/17/35, A.J., 54.
3. At discharge following operation: 12/17/34, L.S., 78; 4/29/35, M.V., 66; 6/1/35, B.M., 108; 6/6/35, A. J., 75.

In the tables which tabulate the results of the present study the column headed "D" records the value of the blood amylase, which term is preferred to the older one, diastase. Table I indicates that hypothyroidism or even myxedema may develop without abnormal

[1] Somogyi, M., PROC. SOC. EXP. BIOL. AND MED., 1936, **32**, 538.

TABLE I.
Effect of Thyroid Feeding on Untreated Hypothyroidism.

Patient			Before				After			
Name	Age	Sex	Date	BMR	D.	daily dose	Date	BMR	D.	
E.S.	53,	♀	12/2/36	—24	168	gr. ii	3/2/37	—	133	much imp.
E.W.	42,	♀	1/7/37	—24	94	iss	2/18	—12	114	” ”
C.S.	41,	♀	1/26	—12	70	ii	3/17	—7	52	unchanged
E.T.	56,	♀	2/12	—8	84	ii	3/23	0	73	much imp.
F.D.	52,	♀	2/11	—12	160	ii	4/17	+14	88	*toxic* 4/17
R.T.	40,	♀	2/17	—24	114	i	4/20	—20	89	imp.
E.L.	45,	♀	3/2	—16	84	ii	4/20	—10	73	sl. imp.
Effect of { increasing / decreasing dose of Thyroid in Hypothyroidism.										
F.H.	32,	♀	12/29/36	—12	145	i→ii	3/2/37	—12	123	imp.
E.B.	26,	♀	1/8/37	—2(?)	114	i→iss	3/16	—11	100	”
H.W.	29,	♀	2/11	—10	123	i→ii	3/23	—9	94	”
H.H.	54,	♀	2/18	—6	47	i→ii	4/20	+12(?)	47	”
K.H.	47,	♀	1/14	—9	46	ii→i	3/4	—16	57	? toxic 1/14
L.D.	35,	♀	4/17	—2	46	ii→i	5/15	—9	55	toxic 4/17

blood amylase values. This must not be taken to mean that values above the normal range may not be found in a larger series of cases since only E.S. and E.W. had spontaneous hypothyroidism, the remainder of the cases being of postoperative hypothyroidism; as will be seen later, the amylase may rise only very slowly following operation and in Table III is recorded a value of 67, two months following operation, at a time when the patient had developed myxedema. Further study of spontaneous hypothyroidism and of very long-standing postoperative hypothyroidism may reveal grossly *elevated* values. The tendency of the blood amylase to fall, however, in response to thyroid medication is unmistakable, only one patient (E.W.) showing a rise. The fall is quite abrupt in F.D., who showed definite thyroid intoxication on 4/17. In the second portion of Table I, H.K. and L.D. show a slight rise after decrease

TABLE II.
Effect of Thyroid Feeding on Neurotic Patients with Questionable Hypothyroidism.

Patient			Before				After			
Name	Age	Sex	Date	BMR	D	daily dose	Date	BMR	D	
M.E.	35,	♀	12/3/36	—16	123	ii	1/15/37	—7	123	no imp.
A.L.	50,	♀	1/6/37	—25	100	iss	1/29	—19	73	” ”
H.R.	39,	♀	1/8	—20	80	ii	1/29	—4	80	” ”
B.H.	47,	♀	2/4	—11	73	i	3/17	—6	88	” ”
M.H.	32,	♀	3/25	—15	123	ii	5/8	—	64	sl. *toxic* 5/8
Effect of decreasing dose in same group.										
G.W.	33,	♀	12/23/36	—2	88	ii→0	1/25/37	—13	88	no change
M.W.	35,	♀	1/5/37	+6	133	ii→i	3/9	—6	100	*toxic* 1/5
M.S.	29,	♀	1/17	+6	50	ii→ss	3/6	—12	55	*toxic* 1/17

of thyroid dosage from 2 grains of desiccated thyroid substance to 1 grain, daily. Patient C.S. was not distinctly hypothyroid in any respect before thyroid feeding was started; she had a recurrence of palpable thyroid tissue some eighteen months after operation for toxic goiter and was given thyroid substance in the hope that further growth of her goiter would be prevented.

In Table II is recorded experience with a group of patients whose well-defined neuroses more or less closely simulated hypothyroidism. These patients were usually given only a short course of thyroid feeding as a therapeutic test (M.E. took thyroid only 3 weeks, as did H.R. and A.L.) and little or no change is seen in these individuals, but M.H., who became mildly thyrotoxic, shows a pronounced fall in amylase. An unexplained rise is seen in one case (B.H.) and an unexplained fall on decreasing the dosage in another (M.W.), although the latter patient was so highly erratic as to somewhat vitiate any conclusions; she also had several severe upper respiratory infections during the period of observation and any intercurrent infection may lower the blood amylase. The time element is of importance here, for in M.E., H.L. and G.W. no change in amylase is noticed over a period of a month or less although the basal metabolism is appreciably altered within this length of time.

TABLE III.
Thyrotoxicosis: Effect of Treatment.

Patient	Unstabilized			Stabilized				Post-operative		
N. Age Sex	Date	BMR	D	Date	BMR	D	Op.	Date	BMR	D
A.H. 46, ♀	12/8/36	+26	59	12/21/36	+14	53	12/22	2/5/37	—4	80
R.M. 61, ♀	12/2		152				12/17 & 28	2/17	—2	230
M.G. 37, ♀	12/3	+30	24	3/17/37	+25	15	3/18 & 26	4/17	—8	29
A.L. 38, ♀	2/4/37	+27	38	2/16	+6	53	2/18	4/21*	—24	67
R.T. 40, ♀				12/30/36	+10	75	1/2/37	2/17*	—24	114
M.V. 20, ♀	2/5	+11	74	3/29/37	—21	100				
D.B. 42, ♀	2/16	+20	123	4/21	+13	145				
A.F. 51, ♂				12/5/36	—1	80	12/10	12/31	—24	84
L.B. 39, ♀				1/8/37	+31	66	1/9	1/15	+7	70
P.B. 46, ♀	2/23	+51	73	4/28	+26	94				

Table III indicates the occasionally very low values that are found in thyrotoxicosis and the tendency for the amylase to rise when important improvement is seen in the basal metabolism and in clinical status. There has not been any apparent difference in the behavior of the amylase in respect to the type of goiter with which the thyrotoxicosis was associated in this small series, solitary adenoma, multinodular goiter and diffuse hyperplastic goiter all being represented. The direction of change is the same for all types, once thyrotoxicosis is established; larger series of cases may reveal

quantitative differences varying with the pathological classification. (In one patient, not included here, C.H., no activity whatever of the serum had occurred after 30 minutes of incubation; this indicates an almost complete lack of activity of the ferment.) Eight determinations were made before operation on patient M.G. over a period of three months during which she was highly refractory to treatment and seemed to be on the verge of thyroid crisis at times. The amylase values were exceedingly low, varying from 15 to 48 during these exacerbations and remissions of her condition. In the first five cases recorded in Table III, the postoperative observations have been made at a sufficiently remote period that the amylase has reached or surpassed the preoperative values, yet M.G. is still far below normal and, as has been noted, A.L. had actually developed myxedema though her diastase had come up only to the lower ranges of normal. R.T. had also developed myxedema though her preoperative figure was not so low as with M.G. and A.L. One would judge from this that the return of the blood amylase to normal lags behind the improvement in other respects, as judged by basal metabolism and the circulatory status. This is also indicated by the preoperative course of A.H. and A.L. and by the early postoperative observations on A.F. and L.B.

TABLE IV.
Behavior of Amylase in Early Post-op. Phase.

Patient			Pre-op.		Post-op.			
				Amylase				
Name	Age	Sex	BMR		8 hr.	24	48	5 d.
G.H.	60,	♂		50	48	53		
temp. F.					98.6	99		
E.J.	27,	♀		52	53	55		
temp.					99	98.8		
P.B.	46,	♀	+26	94	48	47	52	59
temp.					99	100.2	98.6	98.6
G. R.	36,	♀	+16	76	42	35	43	57
temp.					98.6	98.6	98.8	98.6
K.P.	22,	♀	+15	114	84	80		
temp.					99.4	102		
E.S.	47,	♀	+5	73	46	41	66	
temp.					99	99	99.6	

More striking evidence of the importance of the time element and further indication as to the behavior of blood amylase in thyrotoxicosis is furnished in Table IV, in which serial observations are recorded for the immediate postoperative phase, during the period in which an exacerbation of all signs of thyroid intoxication is produced by the operation itself. In thyrotoxic patients a thyroid

crisis in miniature is produced during the first 48 hours after operation; on the other hand, little or no reaction is observed following operations on non-toxic goiters. The two patients in Table IV, G.H. and E.J., who were operated on for non-toxic, encapsulated adenoma of the thyroid, show no variation in the amylase during the immediately postoperative phase although their preoperative levels are low. Quite different is the reaction to operation of the other four patients, P.B., G.R., K.P., and E.S., who were distinctly thyrotoxic and were operated on for diffuse hyperplastic goiter after the usual preparatory treatment. They show an immediate, important fall in blood amylase in observations made 8 hours after operation; this low level is maintained for at least 48 hours and the preoperative level may not have been reached at the time of discharge from the hospital in 5 days. As shown in the table, this process may occur without significant febrile reaction.

There has long been reason to suspect that there was functional impairment of the liver in thyrotoxicosis, though no conclusive evidence as to its constancy or as to the mechanism involved has been available. The occasional jaundice seen in patients dying in thyroid crisis and autopsy findings indicative of hepatitis have not been clearly distinguishable from similar occurrences complicating other febrile forms of exitus; there is much further similarity between the clinical courses of patients in thyroid crisis and in the terminal stages of acute hepatitis in that both are marked by fever, delirium and coma and loss of vasomotor tone with fall in blood pressure. There is ample evidence in the German literature of the last 10 years that the blood lactate rises to abnormal levels and returns very slowly to the resting level after measured exertion in thyrotoxic patients and this has been attributed to improper resynthesis of lactic acid to glycogen on the part of the liver. Finally, the author[2] has reported that death occurs in postoperative thyroid crisis even though an afebrile course be maintained by the employment of a continuous neutral bath; we consider this clear evidence that a metabolic intoxication is the principal factor in thyroid crisis and that it may lead to a fatal issue even though the factor of hypercombustion be controlled. The present work indicates, pending proof to the contrary, that the most important site of disturbed intermediary metabolism is the liver. Whether a derangement of the metabolism of substances other than carbohydrates also occurs will be learned by the anticipated improvement in such other tests of liver function as that of hippuric acid excretion, as advocated by

[2] Bartlett, W., Jr., *Tr. Section Surg., A.M.A.*, 1936.

Quick;[3] there is still controversy as to results obtained by its use in thyrotoxicosis.

Conclusions. Increased thyroid activity is accompanied by decrease in the amount of the blood amylase, and vice versa. There is a pronounced fall in the level of blood amylase within 8 hours following thyroidectomy in thyrotoxic patients; this does not occur after operations for non-toxic goiter. The return of blood amylase to normal values following thyroidectomy lags behind the improvement in clinical status and the restoration of basal metabolism to normal level. These events are considered to be evidence of impaired liver function in thyrotoxicosis.

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Action of Atropin and Eserin on Adrenalin Secretion Caused by KCl and CaCl.*

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The introduction of $CaCl_2$ or KCl into the adrenal circulation is known to cause a secretion of adrenalin (Bacq and Rosenblueth,[1] Feldberg,[2] Katz and Katz[3]). In the present investigation we have endeavored to determine whether this adrenalin secretion in cats can be influenced by previous injections of atropin or eserin, assuming that atropin may decrease the amount of adrenalin secreted upon $CaCl_2$ or KCl injection, while eserin may enhance it. Such results would justify the working-assumption that the salts act on the adrenal medulla by means of an acetylcholin-like transmitter, as has been shown for the action of KCl on other organs such as salivary glands, tongue, sweat glands (Feldberg and Guimarais[4]), or for the transmission of splanchnic stimulation to the adrenals (Feldberg and coworkers[5, 6]).

Our method of recording the adrenalin output effected by the

[3] Quick, A. J., Arch. Int. Med., 1936, **57**, 544.

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[1] Bacq, Z. M., and Rosenblueth, A., *Am. J. Physiol.*, 1934, **108**, 46.

[2] See 4.

[3] Katz, G., and Katz, G., *J. Pharm. and Exp. Ther.*, 1937, **59**, 284.

[4] Feldberg, W., and Guimarais, J. A., *J. Physiol.*, 1936, **86**, 306.

[5] Feldberg, W., and Minz, B., *Pfluegers Arch.*, 1933, **233**, 657.

[6] Feldberg, W., Minz, B., and Tsudzimura, H., *J. Physiol.*, 1934, **81**, 286.