Vit. B_{12} in Thyrotoxicosis and Myxedema.* (23438)

HERMAN ZIFFER,† ARON GUTMAN,‡ INEZ PASHER, HARRY SOBOTKA AND HERMAN BAKER

Department of Chemistry, Endocrine Research Laboratory and Clinic, Departments of Medicine and Chemistry, Mount Sinai Hospital, New York City.

Thyroactive materials fed to animals enhance their vit. B_{12} requirement. This procedure is used in vit. B_{12} assays on chicks to increase the sensitivity of the test(1). Information on how hyper- and hypometabolic states affect B_{12} requirements in man is lacking. We have studied the acute blood responses and urinary excretion of vit. B_{12} in normal, hyperthyroid and myxedematous subjects after an intramuscular (IM) load dose of 50 μg B_{12}.

Materials and methods. The subjects were 6 normal, 10 hyperthyroid and 4 myxedematous patients seen in the endocrine and thyroid clinics and the medical wards of Mount Sinai Hospital. The diagnosis of hyperthyroidism was made clinically and corroborated by the 24-hour radioactive iodine (I^{131}) uptake by the thyroid gland and the protein-bound I^{131} levels in the blood(2) (Table I). Two of the myxedematous subjects (M.S., S.C.2) had undergone surgery for hyperthyroidism, one (F.L.) developed hypothyroidism as a result of treatment with radioactive iodine, and one (R.H.) had myxedema secondary to panhypopituitarism. The normal subjects had no evidence of thyroid disease or chronic debilitating illnesses. No subject was taking vitamin preparations. Diet was not controlled, except that on the day of vit. B_{12} administration the subjects were asked to omit breakfast and to eat a small luncheon. For control purposes, 10 ml of blood were drawn from the antecubital vein of each subject. Fifty μg vit. B_{12} were then given IM and blood was withdrawn at 4- and 8-hour intervals. Urine was collected for 8 hours following vit. B_{12} administration. Whole blood and urine were assayed for vit. B_{12} with *Euglena gracilis*(3,4).

Results. As summarized in Table II, the blood levels of B_{12} at zero ("control") time for the normal and myxedematous subjects were almost the same; 575 and 600 $\mu\mu$g/ml respectively. The hyperthyroid group had a lower control vit. B_{12} blood level with a mean of 320 $\mu\mu$g/ml. There were marked differences in the blood levels of the 3 groups 4 hours after B_{12} administration. The smallest rise was observed in the hyperthyroid group (mean 615 $\mu\mu$g/ml), which was approximately ½ the rise observed in the normal subjects and ⅓ the rise noted in the myxedematous group. At the end of 8 hours, these ratios were still maintained, although the hyperthyroid group had returned to almost the control levels or lower values (Table II).

The 8-hour urinary B_{12} excretion of the 3 groups showed a mean for the normal subjects of 8.2 μg and ½ this for the thyrotoxic group; the hypothyroid group excreted 2 times as much as the normal group.

Discussion. The values for vit. B_{12} given in this study are for whole blood and are 40-

TABLE I. Laboratory Data on Thyrotoxic Subjects.

I^{131} uptake, % tracer dose retained in 24 hr	PBI^{131}, % tracer dose/l plasma, 72 hr‡	Estimated duration of toxicity
80	1.50	8 yr*
70	1.24	2 "
90	.61	2 "
90	1.01	1 "
78	2.10	1 "
57	1.10	1 " †
90	.72	5 "
80	1.00	6 mo
70	.29	2 "
84	.36	2½ yr†

* Subject treated with propylthiouracil from 1950-1952, and relapsed in 1956.

† Nodular goiters; all other subjects had diffuse goiters.

‡ Normal values of PBI^{131} are 0.26% or less of tracer dose/l of plasma.

* Aided by grants from U. S. Public Health Service and National Assn. for Mental Health to Scottish Rite Research Com.

† Trainee, U. S. Public Health Service.

‡ Fellow of Dazian Fn. for Medical Research.

TABLE II. Blood and 8 Hour Urinary Excretion of Vit. B_{12} Levels following a 50 μg IM Load Dose.

Name	0 time, $\mu\mu$g/ml	4 hr, $\mu\mu$g/ml	8 hr, $\mu\mu$g/ml	8 hr urine, μg
Group 1. Normal subjects				
L.M.	450	825	785	8.6
H.Z.	435	705	705	†
A.G.	515	840	600	†
C.Z.	500	1265	690	12.7
E.F.	615	1550	800	9.1
L.M.R.	850	1445	1150	3.8
S.C. 1*	650	1850	1050	6.8
Mean	575	1210	825	8.2
Group 2. Myxedematous subjects				
S.C. 2*	450	1350	1150	20.7
R.H.	450	1700	1400	†
F.L.	760	1250	710	27.5
M.S.	730	2400	2000	7.7
Mean	600	1675	1315	18.6
Group 3. Thyrotoxic subjects				
B.G.	150	200	170	2.9
S.H.	115	200	115	1.7
G.R.	185	330	260	8.4
B.B.	200	550	400	2.1
N.G.	210	475	305	.9
J.B.	220	735	685	4.9
R.C.	350	600	310	3.5
F.N.	450	505	575	3.9
P.S.	525	1000	750	2.9
M.S.	810	1475	520	8.9
Mean	320	605	410	4.0

* S.C. 1, prior to therapy; S.C. 2, three wk after therapy with 100 μg L-triiodothyronine/day.

† Specimen accidentally discarded or not completely collected.

60 $\mu\mu$g/ml higher than those reported for serum(5). It would appear that some of the control blood levels of the hyperthyroid subjects (Table II) approach those seen in untreated pernicious anemia(6).

Blood levels and urinary excretion of vit. B_{12} accurately reflect the intensity of utilization of vit. B_{12}(7,8). As seen in the present study, hyperthyroidism is associated with (*a*) lower initial B_{12} blood levels, (*b*) a small rise after B_{12} administration, and (*c*) low urinary excretion of the vitamin. These results suggest a greater retention and utilization as compared with normals. The myxedematous group had the highest B_{12} levels and greatest urinary excretion *i.e.* the smallest retention and utilization of the vitamin.

The flagellate *Ochromonas malhamensis* has a B_{12} requirement similar to that of higher animals(9,10). When it is subjected to heat stress, its B_{12} requirement is greatly increased (11). This suggests the analogy that the B_{12} system in higher animals is easily upset or inefficient under conditions of metabolic stress.

Summary. The whole-blood B_{12} values in 10 hyperthyroid subjects before and after a load dose of B_{12} were lower than for a normal and a myxedematous group. The mean 8-hour urinary excretion after B_{12} administration in hyperthyroid subjects was considerably lower than in the normal and myxedematous groups. These data suggest that B_{12} turnover and demand is appreciably greater in hyperthyroidism and appreciably lower in myxedema.

We thank Dr. S. Silver of Thyroid Clinic, who kindly made patients available for this study. We are indebted to Department of Physics for I^{131} determinations.

1. Jukes, T. H., and Williams, W. L., in *The Vitamins, vI.*, Sebrell Jr., and Harris, Eds., Academic Press, N. Y., 1954, 421.

2. Newberger, R. A., Silver, S., Yohalem, S. B., and Feitelberg, S., *New England J. Med.*, 1955, v91, 636.

3. Baker, H., Sobotka, H., Pasher, I., and Hutner, S. H., PROC. SOC. EXP. BIOL. AND MED., 1956, v91, 636.

4. Hutner, S. H., Bach, M. K., and Ross, G. I. M., *J. Protozool.*, 1956, v3, 101.

5. Baker, H., Pasher, I., Sobotka, H., Hutner, S. H., Aaronson, S., and Ziffer, H., *Nature*, in press.

6. Niewig, H. O., Faber, J. G., de Vries, J. A., and Kroese, W. F. S., *J. Lab. Chem. Med.*, 1954, v44, 118.

7. Schilling, R. F., *ibid.*, 1953, v42, 860.

8. Cheymol, J., *Produits Pharmaceutiques*, 1956, v11, 1.

9. Ford, J. E., *Brit. J. Nutrition*, 1953, v7, 299.

10. Ford, J. E., and Hutner, S. H., *Vitamins and Hormones*, v13, Academic Press, N. Y., 1955, 101.

11. Hutner, S. H., Baker, H., Aaronson, S., Nathan, H. A., Rodriguez, E., Lockwood, S., Saunders, M., and Petersen, R. A., *J. Protozool.*, in press.

Received July 9, 1957. P.S.E.B.M., 1957, v96.