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John C. Hoak, ... , Glenna L. Fry, Fred L. Benoit

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Research Article

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Effects of Triiodothyronine-Induced Hypermetabolism on Factor VIII and Fibrinogen in Man

JOHN C. HOAK, WILLIAM R. WILSON, EMORY D. WARNER,
ERNEST O. THEILEN, GLENNA L. FRY, and FRED L. BENOIT

*From the Blood Coagulation Research Laboratory and the Departments of
Internal Medicine and Pathology, University of Iowa, College of Medicine,
Iowa City, Iowa 52240*

ABSTRACT Triiodothyronine (liothyronine sodium) (400–500 $\mu\text{g}/\text{day}$ for 14 days) was given to six normal subjects. Factor VIII (antihemophilic globulin) activity increased from 109 to 167% ($P < 0.05$); fibrinogen increased from 344 to 581 mg/100 ml ($P < 0.01$). To test whether the increases in factor VIII activity and fibrinogen were mediated by beta adrenergic receptors, propranolol (20 mg every 6 hr) was given orally to four other normal subjects in addition to triiodothyronine for 14 days. Factor VIII increased from 100 to 161%; fibrinogen increased from 374 to 564% ($P < 0.01$). Factor VIII activity did not change in a severe classical hemophiliac made hypermetabolic with triiodothyronine, but it increased from 39 to 82% in a patient with von Willebrand's disease. Triiodothyronine-induced hypermetabolism increased the incorporation of selenomethionine- ^{75}Se into plasma fibrinogen. These results suggest that the increases in clotting factor activity during triiodothyronine-induced hypermetabolism reflect an effect of increased protein synthesis rather than enhanced stimulation of beta adrenergic receptors.

INTRODUCTION

Elevated factor VIII activity has been reported in patients with thyrotoxicosis (1, 2). In contrast, a significant decrease in factor VIII activity and episodes of clinical bleeding were found in patients with hypothyroidism (2). The coagulation changes seen in hypothyroidism returned to normal after treatment with desiccated thy-

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roid or triiodothyronine, and the increased factor VIII activity in the hyperthyroid patients also returned to normal after antithyroid therapy (2).

Simone, Abildgaard, and Schulman suggested that the elevated levels of factor VIII in hyperthyroidism resulted from increased sensitivity to catecholamines (2). There is evidence in the older literature which suggests that the cardiovascular and metabolic changes in thyrotoxicosis may be a manifestation of increased sensitivity to catecholamines (3–5). More recent studies in animals and man, however, indicate that there is no increased sensitivity to catecholamines in the hyperthyroid state, and that the cardiovascular and metabolic abnormalities result from a direct effect of thyroid hormones (6–10). In preliminary reports, triiodothyronine-induced hypermetabolism in normal subjects was associated with significant increases in both factor VIII and fibrinogen (11, 12). Since the mechanism responsible for these coagulation changes was unknown, the present studies were designed to test the hypothesis that triiodothyronine-induced hypermetabolism causes increases in these coagulation factors by enhanced stimulation of beta adrenergic receptors. The present report also involves a study of the effects of triiodothyronine upon factor VIII activity in patients with congenital deficiencies of factor VIII.

METHODS

Subjects. The subjects in this study were 16 men from the Iowa State Penitentiary, Fort Madison, Iowa. In addition, four patients at University Hospitals were studied. We obtained informed consent from each individual. All subjects and patients were hospitalized in the Clinical Research Center, University Hospitals, Iowa City. None had clinical or laboratory evidence of thyroid or cardiac disease.

Each subject received a high caloric diet ranging from 2500 to 5000 calories throughout the study.

Duplicate coagulation studies were done in each subject at three separate times. The first studies were performed before treatment with triiodothyronine; the second set of studies was done after 14 days of treatment with triiodothyronine, 400–500 $\mu\text{g}/\text{day}$; the third set of studies represented a post-treatment control and was performed 21 days after triiodothyronine had been discontinued. Body weight and radial pulse rates during sleep were measured daily. The average weight and the average sleeping pulse rate for the last 3 days of each period, oxygen consumption, serum cholesterol, and clinical evaluation were used as indexes of the subject's metabolic state.

Six of the subjects received only triiodothyronine while four subjects received the beta adrenergic blocking agent, propranolol, 20 mg every 6 hr orally, in addition to triiodothyronine.

The effects of D-thyroxine, 3–8 mg/day orally, and L-thyroxine, 3 mg/day orally, upon factor VIII and fibrinogen concentrations were studied in two other subjects.

The effects of triiodothyronine-induced hypermetabolism upon factor VIII activity were also studied in one patient with classical hemophilia, another with von Willebrand's disease, and in one patient who had undergone splenectomy for idiopathic thrombocytopenic purpura 2 yr earlier.

Blood samples. Blood was obtained from subjects and patients in the fasting state by venipuncture with disposable needles and plastic syringes. Blood was added immediately to citric acid-sodium citrate anticoagulant (9.6 g of citric acid, 14.7 g of sodium citrate in 100 ml of aqueous solution titrated to pH 4.7) in a siliconized glass centrifuge tube in a ratio of 9.9 parts blood to 0.1 part anticoagulant. The blood was then centrifuged for 20 min at 4000 rpm at 4°C in an International refrigerated centrifuge. The plasma was separated immediately and transferred to siliconized glass tubes. The plasma was frozen and stored at -20°C . The pH of the stored plasma was 7.4. Samples were tested within 48 hr.

Coagulation studies. Factor VIII (antihemophilic globulin, [AHG]) was assayed in a Celite-activated partial thromboplastin time system with substrate plasma from a patient with severe classical hemophilia (13). In this assay, described originally for factor IX, the use of factor VIII-deficient plasma as substrate in place of factor IX-deficient plasma provides an equally accurate estimate of factor VIII activity. Celite was used as 3% suspension in Tris-saline buffer, pH 7.05. The activity of the partial thromboplastin (Thrombofax)¹ was verified before each experiment by performing a partial thromboplastin time on normal plasma. A dilution curve was prepared by use of pooled normal plasma. The clotting time of the assay mixture when no normal plasma was added represented 0% factor VIII activity. When the normal plasma content of the assay mixture was 100%, the clotting time of this mixture represented 100% factor VIII activity. Fibrinogen concentration was determined by the method of Ratnoff and Menzie (14).

Studies were performed to determine whether the measured increase in factor VIII activity was actually due to factor VIII. The increase in factor VIII activity of a classical hemophilic was measured after transfusion with fresh plasma from two hypermetabolic subjects and was compared with the calculated increase based on the formula of Shanbrom and Thelin (15). (Expected factor VIII increase in

per cent of normal = units administered/body wt in kg \times 0.4.) One factor VIII unit is defined as the activity present in 1 ml of fresh normal pooled human plasma with 100% factor VIII activity. In addition, an incubation experiment with an inhibitor against factor VIII was performed to compare the neutralizing effect of plasma from hypermetabolic subjects with that of plasma taken when the subjects were euthyroid.

The effect of epinephrine (4.2 $\mu\text{g}/\text{kg}$ of body weight over a 30 min period i.v.) on plasma factor VIII and fibrinogen concentrations was studied in one subject during the euthyroid and hypermetabolic periods and in the splenectomized patient. Plasma free fatty acid concentrations were determined by the method of Trout, Estes, and Friedberg (16).

Selenomethionine-⁷⁵Se incorporation into fibrinogen. The incorporation of selenomethionine-⁷⁵Se² into plasma fibrinogen was studied in four additional subjects. The first study was performed when the subjects were hypermetabolic. The second study was done when the subjects returned to their usual metabolic state 3 wk after triiodothyronine had been stopped. Fasting subjects received 25 μC of selenomethionine-⁷⁵Se intravenously at the time each study was performed. Citrated blood samples were obtained before, 1/2, 1, 2, 3, 4, 6, and 24 hr after the injection of labeled methionine.

Fibrinogen was separated by a modification of the procedure described by McFarlane (17). Fibrinogen was first precipitated by addition of 11.5% sodium sulfate solution. The precipitate was dissolved in saline-citrate phosphate buffer, pH 6.0, and reprecipitated with 11.5% sodium sulfate. The precipitate was then dissolved in 0.5 ml of the saline-citrate buffer. To 0.5 ml of the resulting solution, 10 U of thrombin, 0.2 ml of 0.25 M calcium chloride, and 125 mg of epsilon aminocaproic acid were added. The fibrin clot which formed was washed three times with 0.9% saline and then was dissolved in 1 ml of 10% sodium hydroxide and was heated in a water bath at 100°C for 10 min. After cooling, the sample's radioactivity was determined by use of a Picker well-counter. The fibrinogen content of the counted sample was determined by the method of Ratnoff and Menzie (14). Plasma fibrinogen was also measured in each blood sample, and this value was compared with the fibrinogen content of the counted samples. Corrections were made for fibrinogen which had been lost in the separation procedure. This procedure provided an accurate estimate of the rate of incorporation of selenomethionine-⁷⁵Se into plasma fibrinogen.

RESULTS

Direct effects of triiodothyronine. Daily administration of triiodothyronine for 14 days produced a hypermetabolic state in all subjects as indicated by marked increases in sleeping pulse rate and in oxygen consumption, weight loss despite increased food consumption, and a decrease in levels of serum cholesterol. The sleeping pulse rate increased from $72 \pm (\text{SE}) 1$ to 96 ± 3 beats/min. Oxygen consumption increased from 135 ± 4 to 201 ± 8 ml/min per m^2 . Body weight decreased from 168 ± 12 to 162 ± 10 lb. Serum cholesterol decreased from 249 ± 25 to 123 ± 7 mg/100 ml. The magnitude of

² Selenomethionine-⁷⁵Se was obtained from Amersham-Searle, Chicago, Ill. The solution contained approximately 0.06 mg of L-methionine/1 ml, and had a specific activity of 4.5 mc/mg.

¹ Ortho Pharmaceutical Corporation, Raritan, N. J.

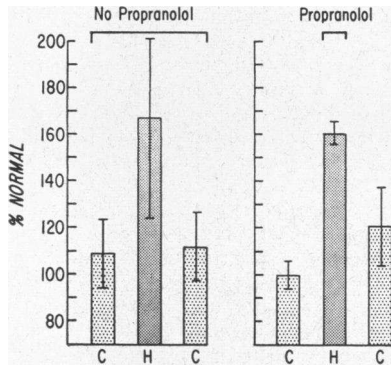


FIGURE 1 Factor VIII activity after triiodothyronine. Values are means \pm SE. C, control period; H, hypermetabolic period. Values of both groups during the hypermetabolic period were significantly different from the controls, ($P < 0.05$), but not from each other.

the changes which occurred in the subjects treated with propranolol and triiodothyronine was similar to that observed in those who received triiodothyronine alone. In the group which received propranolol in addition to triiodothyronine, the sleeping pulse rate increased from 70 ± 3 to 93 ± 4 beats/min. Oxygen consumption increased from 109 ± 6 to 164 ± 2 ml/min per m^2 . Body weight decreased from 162 ± 9 to 153 ± 7 lb. Serum cholesterol decreased from 220 ± 28 to 125 ± 13 mg/100 ml. Each of the subjects developed various symptoms and signs of hypermetabolism. Nervousness, palpitation, tremor, and increased irritability were prominent in the majority of subjects. The clinical manifestations of hypermetabolism disappeared in each subject within 10 days after triiodothyronine was stopped, and the serum cholesterol and oxygen consumption values were normal 3 wk later.

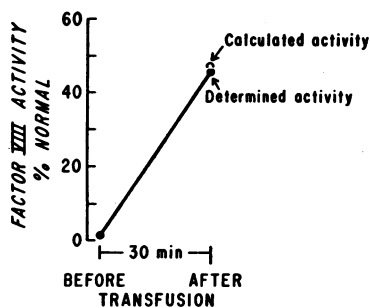


FIGURE 2 Effect of transfusion of plasma from hypermetabolic subjects to a classical hemophiliac. The measured increase in the factor VIII activity of the hemophiliac's plasma corresponded to the calculated increase determined by the assay of the donor plasma. This study suggests that the measured increase in factor VIII induced by triiodothyronine was actually due to VIII rather than to a nonspecific procoagulant.

TABLE I
Incubation Studies with an Anticoagulant
Against Factor VIII

Plasma	Factor VIII activity % normal
Patient with anticoagulant against VIII	2.5
Normal subject a. Euthyroid	90
b. Hypermetabolic	146
Anticoagulant against VIII + euthyroid	35
Anticoagulant against VIII + hypermetabolic	62

0.5-ml samples of plasma from a subject, taken when he was euthyroid and when he was hypermetabolic, were incubated with 0.1 ml of plasma from a patient with an anticoagulant against factor VIII for 60 min at 37° C and then assayed for VIII activity. In the control studies above, 0.1 ml of imidazole-buffered saline was used in place of a second plasma sample

Effect on factor VIII activity (Fig. 1). Both groups of patients developed similar increases in factor VIII activity during the hypermetabolic period. Simultaneous treatment with the beta adrenergic blocking agent, propranolol, did not prevent the increase in factor VIII activity associated with hypermetabolism.

Evidence that the measured increase in factor VIII activity was actually due to factor VIII rather than to a nonspecific procoagulant effect was provided by two types of experiments. First, fresh plasma was prepared from two hypermetabolic subjects and was given to a patient with classical hemophilia over a 30 min period. The *calculated increase* in factor VIII of the recipient's plasma, based on the factor VIII activity and volume of the donor plasma, was essentially the same as the *measured increase* in the recipient's plasma after transfusion (Fig. 2). In another group of experiments, plasma samples taken when a subject was euthyroid and when he was hypermetabolic were incubated with plasma from a patient with an acquired anticoagulant against factor VIII and then assayed for VIII activity (Table I). In this experiment the amount of residual factor VIII ac-

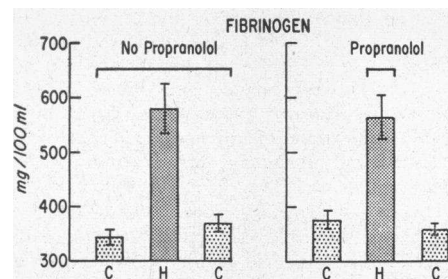


FIGURE 3 Fibrinogen concentrations after triiodothyronine. Values are means \pm SE. C, control period; H, hypermetabolic period. Values of both groups during the hypermetabolic period were significantly different from the controls, ($P < 0.01$), but not from each other.

tivity after incubation is an indirect measurement of the neutralizing effect of the anticoagulant against VIII by the factor VIII in the original plasma sample. The sample taken when the subject was hypermetabolic had a greater neutralizing effect against the circulating anticoagulant than did the sample taken when the same subject was euthyroid.

Effect on fibrinogen (Fig. 3). Propranolol did not prevent the increases in fibrinogen which occurred during hypermetabolism. The increases were significantly different from their respective controls but not from each other.

Beta adrenergic receptor blockade. Evidence for beta adrenergic blockade produced by propranolol in the four hypermetabolic subjects was demonstrated by the response to infusions of isoproterenol. Isoproterenol, 0.05 $\mu\text{g}/\text{kg}$ per min for 4 min i.v., in the absence of propranolol, produced a significant increase in heart rate, from 100 to 140 beats/min ($P < 0.02$) and a significant decrease in diastolic blood pressure, from 65 to 50 mm Hg ($P < 0.05$). These effects were blocked when the subjects were pretreated with propranolol before the isoproterenol infusion. Heart rate increased from 95 to 98 beats/min (NS), and diastolic blood pressure decreased from 64 to 61 mm Hg (NS).

Effects of D-thyroxine and L-thyroxine (Figs. 4 and 5). To test whether the increases in factor VIII and fibrinogen were due to the thyroxine molecule or induced hypermetabolism, D-thyroxine was given to two subjects over a 5 wk period at doses of 3 and 8 mg/day. The usual clinical and laboratory signs of hypermetabolism did not appear, and no significant change occurred in clotting factor concentrations. When D-thyroxine was replaced by

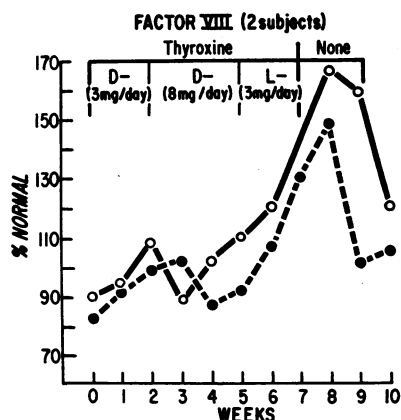


FIGURE 4 Effects of D-thyroxine and L-thyroxine on factor VIII activity. D-thyroxine had little or no effect on factor VIII activity and did not produce hypermetabolism. L-thyroxine caused the subjects to become hypermetabolic, and factor VIII activity increased.

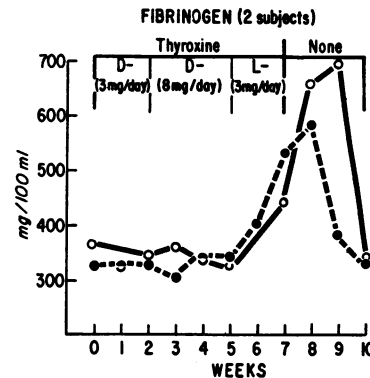


FIGURE 5 Effects of D-thyroxine and L-thyroxine on fibrinogen concentrations. D-thyroxine caused no change in fibrinogen. L-thyroxine caused an increase in the plasma fibrinogen in association with the period of hypermetabolism.

L-thyroxine (3 mg/day), hypermetabolism was induced, and there was a marked increase in factor VIII and fibrinogen concentrations.

Effect of epinephrine infusions. The effects of epinephrine infusions upon factor VIII and plasma free fatty acid (plasma FFA) concentrations were studied in one subject during euthyroid and hypermetabolic periods to determine whether the hypermetabolic state enhanced the increase in factor VIII produced by catecholamines. The studies were repeated in the same subject in both periods to evaluate the effect of pretreatment with propranolol. Hypermetabolism produced an increase in factor VIII activity and in plasma FFA. Factor VIII activity increased from 100 to 142%, and plasma FFA increased from 510 to 723 $\mu\text{Eq}/\text{liter}$. The increases in factor VIII activity and in plasma FFA produced by epinephrine infusion were greater when the subject was euthyroid. During the control period, epinephrine caused the factor VIII activity to increase from 100 to 206% and the plasma FFA to increase from 510 to 1772 $\mu\text{Eq}/\text{liter}$. During the time when the subject was hypermetabolic, epinephrine caused the factor VIII activity to increase from 142 to 184% and the plasma FFA to increase from 723 to 1465 $\mu\text{Eq}/\text{liter}$. Propranolol attenuated the increase in factor VIII and plasma FFA produced by epinephrine during the control and hypermetabolic periods. During the control period after pretreatment with propranolol, epinephrine caused the factor VIII activity to increase to only 121%, and the plasma FFA concentration was 669 $\mu\text{Eq}/\text{liter}$. When a similar study was performed during the hypermetabolic period, the factor VIII activity increased to only 158%, and the plasma FFA concentration increased to 914 $\mu\text{Eq}/\text{liter}$.

Effects of triiodothyronine after splenectomy. When hypermetabolism was produced by triiodothyronine in a patient after splenectomy, both factor VIII activity and

TABLE II
Incorporation of Selenomethionine-⁷⁵
into Plasma Fibrinogen

Time after injection of selenomethionine	Counts per minute in fibrinogen from 1 ml plasma		P value
	Euthyroid period	Hypermetabolic period	
hr			
0.5	9 ± 3	25 ± 2	<0.05
1	66 ± 10	150 ± 14	<0.02
2	174 ± 7	262 ± 33	<0.05
3	227 ± 12	311 ± 26	<0.05
4	235 ± 10	327 ± 39	<0.05
6	231 ± 14	368 ± 32	<0.01
24	266 ± 9	308 ± 26	NS

Values represent means ± SE from studies performed in four subjects made hypermetabolic with triiodothyronine. NS = not significant at 5% level.

fibrinogen concentrations increased in association with an increase in pulse rate and a decrease in serum cholesterol. Factor VIII activity increased from 98 to 200%, and the fibrinogen level increased from 350 to 490 mg/100 ml. Pulse rate increased from 80 to 115 beats/min, and the serum cholesterol decreased from 190 to 120 mg/100 ml. A similar increase in factor VIII activity occurred when the same patient was given epinephrine when she was euthyroid, but the fibrinogen level remained essentially unchanged. Scanning of the abdomen after intravenous injection of damaged erythrocytes, labeled with technetium-99, failed to demonstrate an accessory spleen.

Effect of hypermetabolism in hemophilia and von Willebrand's disease. When a patient with severe classical hemophilia was treated with triiodothyronine, he developed the usual clinical and laboratory finding of hypermetabolism, but no change was noted in factor VIII activity. In a patient with von Willebrand's disease, however, factor VIII increased from 39 to 82% during the period of induced hypermetabolism.

Incorporation of selenomethionine-⁷⁵Se into fibrinogen (Table II). In four subjects, the rate of incorporation of selenomethionine-⁷⁵Se into plasma fibrinogen was determined during the hypermetabolic and euthyroid periods. The amount of the labeled amino acid incorporated into fibrinogen was significantly greater during the first 6 hr when the subjects were hypermetabolic.

DISCUSSION

The findings in this study of triiodothyronine-induced hypermetabolism support the findings of others who found increased factor VIII activity in patients with spontaneous thyrotoxicosis (1, 2). In addition they demonstrate clearly that plasma fibrinogen concentrations increased under the influence of thyroid hormones.

Simone, Abilgaard, and Schulman did not report elevated fibrinogen concentrations in their patients with thyrotoxicosis, but two of their patients had values over 400 mg/100 ml (2). Unfortunately, they did not report the effect of antithyroid therapy upon fibrinogen levels in their thyrotoxic patients. In our study in which each subject served as his own control, we were able to document changes in fibrinogen as well as in factor VIII during the hypermetabolic period.

If the changes in factor VIII activity in triiodothyronine-induced hypermetabolism are related in increased sensitivity to catecholamines, adequate blockade of beta receptors might be expected to prevent the usual increase in factor VIII and fibrinogen levels. Adequate beta receptor blocking doses of propranolol did not inhibit these effects in the subjects with hypermetabolism. Epinephrine causes an increase in factor VIII activity in man (18). This effect can be prevented by pretreatment with the beta adrenergic receptor blocking agent, propranolol, but not by phentolamine, an alpha receptor blocker (18). Epinephrine, unlike triiodothyronine, does not produce an increase in the plasma fibrinogen concentration. In an additional study, a greater increase in factor VIII developed in response to epinephrine when the subject was euthyroid than after a similar infusion when he was hypermetabolic.

An intact spleen does not appear necessary for the increase in factor VIII and fibrinogen since a normal response was observed in a splenectomized patient who was given triiodothyronine. D-thyroxine had little or no effect on factor VIII or fibrinogen concentrations, but a response similar to that obtained with triiodothyronine was observed when normal subjects were made hypermetabolic with L-thyroxine. As might be expected from the known differences in onset and duration of metabolic effects produced by thyroxine in comparison to triiodothyronine, L-thyroxine was slower in producing increases in factor VIII and fibrinogen, and these effects persisted for a considerable period after the drug was stopped. A patient with classical hemophilia did not show improvement in factor VIII activity during triiodothyronine-induced hypermetabolism. In contrast, a patient with von Willebrand's disease demonstrated a rise in factor VIII activity after triiodothyronine. Increases in factor VIII activity and fibrinogen have also been seen in disease states (19), after injections of fever-producing vaccines (19) and after fever induced by intramuscular injections of blood (20) or milk (21). It appears that individuals who have the capacity to synthesize factor VIII and fibrinogen will demonstrate increases in these factors in response to hypermetabolism.

The selenomethionine-⁷⁵Se studies showed increased incorporation of labeled methionine into plasma fibrinogen during the period of hypermetabolism. Since no infor-

mation was available concerning precursor pool size or survival of fibrinogen, the suggestion that increased incorporation of methionine into fibrinogen represents enhanced fibrinogen synthesis must be made with caution. It is unlikely, however, that a prolonged life span of fibrinogen accounts for the findings during the hypermetabolic period. Survival of clotting factors is increased in myxedema and decreased in thyrotoxicosis when further synthesis is blocked by coumarin drugs (22). The biological half-life of fibrinogen was increased in a patient with myxedema and decreased in a patient with fever (23). Kekki found that in experimental hyperthyroidism albumin synthesis and catabolism were strongly accelerated, whereas a distinct decrease in albumin metabolism was noted in hypothyroidism (24). The catabolism of gamma globulin was affected by thyroid hormone stimulation in a similar way (24). A similar effect of thyroid hormone upon albumin synthesis and degradation has been observed in man (25). We believe that the findings in the present study suggest that fibrinogen synthesis was increased in the subjects during the period of hypermetabolism. Since there are complex interrelationships between hormones, nutrition, and hepatic enzyme activity, however, the concept that excess thyroid alters protein metabolism quantitatively as a primary effect may have to be altered in the future. Increases in the uptake of selenomethionine-⁷⁵Se into fibrinogen were also found by Awwad, Potchen, Adelstein, and Dealy when patients were pretreated with triiodothyronine for 4 days before parathyroid scanning was performed (26).

Our results do not support the hypothesis that the increased concentrations of factor VIII and fibrinogen observed as an effect of excess thyroid hormone reflect an effect of enhanced stimulation of beta adrenergic receptors. Rather, it seems more likely that they may represent another manifestation of increased protein synthesis which is known to occur in hypermetabolism induced by thyroid hormones.

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