TABLE III.

Fibrinolytic Activity of Globulin Fraction III-3 After Incubation with Thrombin at 38°C.

Thrombin dilution	Incubation time (hr) 0	1	2
1:1	7′	17′	53′
1:2	6′	13′	46′
1:4	6′	12′	46′
1:8	5′	23′	>4°
No thrombin added	5′	4°38′	>4°

Body of table gives lytic times in hours (°) and minutes (′).

Incubation mixture: 2 ml thrombin + 2 ml (= 2 mg) globulin III-3.

Fibrinolysis test: 0.5 ml incubation mixture + 1 ml saline + 0.2 ml 1:10 thrombin + 1 ml 0.6% fibrinogen.

thrombic activity due to the presence of a small amount of thrombin in this fraction.[10]

Table II shows the results of a similar experiment carried out with the fibrinolysin preparation. Here again it is evident that the stability of thrombin was not affected by the presence of fibrinolysin. All of the clots obtained at the 21-hour testing period were completely lysed within 24 hours; and those obtained at the 46-hour testing period were completely lysed within 54 hours, showing that active fibrinolysin was still present. However, the mixtures containing the highest concentrations of thrombin retained the greatest amount of fibrinolytic activity. The shortest lytic time (after the 46-hour incubation period) was 4 hours for the 1:2 dilution of thrombin; 9 hours for the next higher dilution; and progressively longer lytic times were observed up to a maximum of 54 hours for the sample which contained no thrombin. These observations were checked using globulin fraction III-3 in place of the fibrinolysin preparation, and the results of these lytic time measurements are given in Table III. It can be seen that the solutions containing the higher concentration of thrombin retained their fibrinolytic activity better than samples with little or no thrombin present.

Summary. It has been shown that fibrinolysin does not affect the clotting activity of thrombin, and that the thrombin preparation increased the stability of fibrinolysin under the conditions of these experiments.

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Effect of Iodine and Adrenalin on Thyrotropin in Graves' Disease and in Normal and Thyroidectomized Dogs.

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This study deals with (1) the evaluation of the amount of circulating thyrotropic factor in clinical hyperthyroidism, (2) the effect of iodine on such circulating thyrotropic factor, and (3) the influence of the parenteral injection of adrenalin on thyrotropic discharge from the anterior pituitary in the intact and the totally thyroidectomized experimental animal.

Method. Biological assay was used for the determination of thyrotropic factor. This technic involves histological examination of the thyroids of young guinea pigs not exceeding 200 g in weight, following subcutaneous injection of 5 cc of serum from the patient or experimental animal. The guinea pigs were injected on 2 successive days and were killed with ether 24 hours after the last injection. The thyroid lobes were then removed, fixed in 10% formalin, and stained with hematoxylin-eosin. The thyroids were then examined for hyperplastic changes. Following the injection of varying amounts of pure thyrotropic factor there occur changes in the thyroid characterized by a decrease in the amount of colloid in the follicles, an in-

crease in the height of the cells lining the acini, a decrease in the size of the alveoli, and not infrequently mitosis may be observed.[1-4] These findings are not dissimilar to those observed in the thyroids of patients with Graves' disease. The amount of circulating thyrotropic factor in the serum of our patients and experimental animals was determined on the basis of the criteria just outlined.

Specimens of blood were obtained from patients with Graves' disease before treatment and again on the 2nd, 4th, 6th, 8th, and 11th days after lugolization was started. Five cc of the serum was injected into the guinea pigs on 2 successive days. The animals were killed 24 hours later and their thyroids promptly removed. On several patients samples of blood were also obtained on the 2nd, 4th, and 6th days, after subtotal thyroidectomy. The animal experimental studies were conducted in dogs. Normal dogs were injected with 1 cc of adrenalin-in-oil twice daily. On the 4th day of therapy one lobe of the thyroid was removed for histologic study. The injections were continued and the second lobe of the thyroid was removed 10 days later. In another group of animals a control sample of blood was obtained, a total thyroidectomy performed, and injections of 1 cc of adrenalin-in-oil twice daily were then begun. Specimens of blood were obtained on the 2nd, 4th, 6th, 8th, and 10th days after thyroidectomy. Five cc of serum was injected into the guinea pigs on 2 successive days and the guinea pigs' thyroids were removed 24 hours later.

Results. Thirteen patients with Graves' disease were studied in this fashion. In all these patients prior to treatment there was less circulating thyrotropic factor than is found to be present in normal individuals. This is consistent with the observation previously reported by Rawson and Starr.[4] Following lugolization there occurred an increase in circulating thyrotropic factor in all patients, which reached a peak between the 4th and 6th days and then began to diminish. In 3 instances the increase in circulating thyrotropic factor was marked, as evidenced by the profound hyperplastic changes observed in the guinea pig thyroids. In the remaining 10 patients the increase in circulating thyrotropic factor varied from slight to moderate. In a control series of 6 normal individuals who were given Lugol's solution and studied in an identical manner there occurred a barely perceptible increase in circulating thyrotropin. After subtotal thyroidectomy in patients with Graves' disease there occurred a further slight increase in the thyrotropic factor in the blood. This confirms the observations of Rawson and Starr,[4] who noted a similar although much more marked increase after *total* thyroidectomy.

Following the injection of adrenalin-in-oil in the intact dogs there occurred marked hyperplastic changes in the thyroid lobe removed on the 4th day of injection. The further administration of adrenalin-in-oil resulted in a considerable decrease in the hyperplasia of the remaining lobe which was removed 10 days later.

In the totally thyroidectomized dogs the injection of adrenalin-in-oil resulted in a marked increase in circulating thyrotropic factor, which reached its peak approximately 4 to 6 days after the beginning of treatment and thereafter began to diminish.

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[4] Rawson, R. W., and Starr, P., *Arch. Int. Med.*, 1938, **61**, 726.