Failure of Short-term Administration of Thyrotrophic Hormone to Produce Exophthalmos in Man.* (20553)

BENJAMIN SIMKIN AND PAUL STARR.

From the Department of Medicine, University of Southern California, School of Medicine, and the Thyroid Clinic, Los Angeles County General Hospital.

It is widely held that thyrotrophic hormone (TSH) is the cause of human exophthalmos, but this has never been directly proven by experimental observation. This opinion is based upon the development of exophthalmos in several species of animals following the administration of various TSH preparations (1). To our knowledge there are no published reports on the exophthalmic potency of TSH in man. It is the purpose of this report to show that the short-term administration of thyroid stimulating doses of certain TSH preparations does *not* cause exophthalmos in man.

Methods and procedure. In the course of clinical studies on the use of TSH injections as a means of differentiating pituitary from primary hypothyroidism in patients(2), serial quantitative measurements of the amount of protrusion of the eyeballs of these patients were obtained before, during and after the administration of the hormone. Exact measurement of proptosis was accomplished with the aid of the Hertel exophthalmometer. One of us (B.S.) obtained all of the readings. Measurement of proptosis was made daily during the administration of TSH, and each daily measurement represented the average of 3 readings with the exophthalmometer.

In this study, exophthalmometer readings were obtained in 3 groups of patients. The *control* group consisted of 14 untreated patients in whom 2 daily consecutive exophthalmometer measurements were made. The second group consisted of 5 patients who had *intact thyroid glands* capable of functioning; all 5 of these patients had a marked increase in radioactive iodine uptakes by their thyroid glands following the administration of TSH (Table I). Two of these patients had pituitary hypothyroidism and the other 3 patients were euthyroid. The third group consisted of 8 *athyreotic* hypothyroid patients; these patients were proved to be athyreotic by failure of their thyroid glands to be stimulated by TSH injections (Table I). The 13 patients in the last 2 groups received daily doses of 25 or 30 mg of TSH by intramuscular injection for from 3 to 22 days. This dose of TSH was found to be thyroid-stimulating in those patients with intact thyroid glands. Nine patients received a Parke-Davis TSH preparation, Lot No. 50P5; 3 patients received a preparation of Armour TSH, Lot No. K26002; and one patient was given Armour TSH, Lot No. K39405.†

Results and discussion. Two daily consecutive exophthalmometer measurements in the 14 *untreated control* patients resulted in a mean change in readings of —0.014 ± 0.096 mm ($p = 0.88$). The administration of TSH to the group of 5 patients with *intact thyroid glands* and to the group of 8 *athyreotic* patients resulted in mean changes in exophthalmometer reading of —0.119 ± 0.102 mm ($p = 0.24$) and +0.033 ± 0.075 mm ($p = 0.67$), respectively. These data show that the administration of TSH to patients both with or without intact thyroid glands caused no greater changes in exophthalmometer readings than those observed upon 2 consecutive daily readings in the untreated or control group. In short, thyroid-stimulating doses of TSH did *not* produce exophthalmos in our patients under the conditions of this experi-

* This investigation was supported in part by a research grant from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service, by a research grant from the California Division of the American Cancer Society, and by a grant from the Parke-Davis & Co.

Presented at 5th Meeting, Western Society for Clinical Research, Carmel, Calif., Jan. 25, 26, 1952.

† We would like to thank the Parke-Davis & Co., and the Armour Laboratories for supplying us with TSH preparations used in this study.

TABLE I. Effect of TSH on Thyroid I^{131} Uptake.

Thyroid intact				Athyreotic			
	Thyroid I^{131} uptake				Thyroid I^{131} uptake		
No. of days of TSH	Before TSH	After TSH	Incr. I^{131} uptake	No. of days of TSH	Before TSH	After TSH	Incr. I^{131} uptake
3	7%	65%	+58%	12	4%	3%	—1%
5	5	69	+64	3	0	0	0
5	21	44	+23	5	3	2	—1
3	19	42	+23	5	2	3	+1
22	1	14	+13	5	17	23	+6
				3	10	15	+5
				5	3	5	+2
				11	0	1	+1
Mean	10.6	46.8	+36.2	Mean	4.9	6.5	+1.6

ment and with the particular TSH preparations used.

These results are contrary to previous animal observations in which anterior pituitary preparations with thyrotrophic activity induced exophthalmos in the guinea pig, rabbit, and a fish (Fundulus), within a time period of 24 to 72 hours. Possible explanations for this discrepancy are: 1) the dose of TSH given to our patients was too small; 2) TSH was not administered to our patients for a long enough period of time; 3) there is a species difference in the ability of the orbital tissues to respond to TSH; 4) there may be differing degrees of exophthalmic potency of various TSH preparations; and consequently, 5) exophthalmos may be caused by a pituitary exophthalmic factor which is *not* TSH but which is closely associated with it when whole pituitaries are fractionated by chemical means. We have not been able to test the first 3 points as yet, but plan to do so in the future. Concerning the last 2 points, Dobyns(3) has shown that there may be differing degrees of exophthalmic potency of various TSH preparations, and studies by Jefferies(4) on the inactivation of TSH with iodine suggest that the pituitary exophthalmic factor may not be identical to thyrothrophic hormone.

Summary. The parenteral administration of thyroid stimulating doses of 3 thyrothrophic hormone preparations in 13 patients both with and without thyroid glands for from 3 to 22 days failed to cause any statistically significant increase in proptosis. Under the conditions of this experiment, the short-term administration of TSH did not cause exophthalmos in man.

We are indebted to Dr. Frederick Moore, University of Southern California, School of Medicine, for the statistical analysis of the data.

1. Dobyns, B. M., *J. Clin. Endocrinol.*, 1950, v10, 1202.

2. Starr, P., Simkin, B., Unpublished studies.

3. Dobyns, B. M., *S. G., and O.*, 1946, v82, 290.

4. Jefferies, W., McK., *J. Clin. Endocrinol.*, 1949, v9, 927.

Received May 26, 1953. P.S.E.B.M., 1953, v84.