THE EFFECT OF ATROPINE AND SCOPOLAMINE ON THE SUBSEQUENT INJECTION OF EPINEPHRINE IN THYROTOXIC AND EUTHYROID PATIENTS *

STANLEY J. SARNOFF, M.D.,† AND OLIVER COPE, M.D.

Boston, Massachusetts

Received for publication September 17, 1953

NUMEROUS studies have demonstrated the increased response to the administration of epinephrine in the experimental animal given thyroxin (1, 4–8, 10, 11). It has also been shown that when atropine is given prior to the administration of epinephrine, the latter produces a greater effect on pulse rate and blood pressure than would otherwise occur (3, 13). In the year before the gathering of the data presented below, 4 thyrotoxic patients, whose basal metabolic rate had been brought to normal or near normal levels, exhibited a reaction of appreciable proportions during operation. Each had received atropine as premedication. Lee (10) has demonstrated that a decrease in the basal metabolic rate toward normal is not accompanied by a correspondingly prompt return toward normal of the epinephrine sensitivity of sympathetic effector organs.

Atropine, together with morphine, is commonly administered to thyrotoxic patients just before operation at a time when they are most apprehensive and might logically be expected to secrete significant amounts of epinephrine. Accordingly, it was thought worth while to ascertain whether or not a given dose of epinephrine produces a more marked effect after atropine has been administered. It was also thought worth while to make a quantitative comparison of atropine and scopolamine in this regard in both euthyroid and thyrotoxic patients.

THE EFFECT OF ATROPINE MATERIAL AND METHOD

All observations were made on patients of the Massachusetts General Hospital. Table 1 sets forth the drugs that were administered to each of these patients, the route of administration, the dose given and whether or not the patients were thyrotoxic. Five were males and 9 were females. The ages ranged from 15 to 51, the average age being 30 years. The nonthyrotoxic group of patients were selected from available preoperative or convalescent patients; they were in the hos-

* From the Department of Surgery of the Harvard Medical School and the Surgical Services at the Massachusetts General Hospital.

† Present address is Department of Physiology, Harvard School of Public Health, Boston.

pital for inguinal herniorrhaphies, interval appendectomies or hemorrhoidectomies and were in good nutritional condition.

Two or more sets of observations were made on each patient. Preceding each observation period the patient rested, flat in bed, for thirty minutes. The blood pressure was determined by the auscultatory method, adhering to the criteria of Ragan and Bordley (12). Pulse rates were counted for a full minute with the aid of a stop watch and counting was started during the resting phase of expiration.

All the epinephrine hydrochloride used in these experiments was from the same box of 100 ampules. The Parke-Davis product was employed. The atropine sulfate was procured from the wards at the time of the experiment.

TABLE 1

PATIENTS, DRUG, DOSE AND ROUTE OF ADMINISTRATION

Case	Observation 1		Observation 2				Thyrotoxic or Control
	Epinephrine, Route	Dose in mg.	Atropine, Route	Dose in mg.	Epinephrine, Route	Dose in mg.	
1	S.C.	0.3	I.V.	0.64	S.C.	0.3	Thyrotoxic
2	S.C.	0.3	I.V.	0.64	S.C.	0.3	Thyrotoxic
3	S.C.	0.3	I.V.	0.64	S.C.	0.3	Thyrotoxic
4	S.C.	0.3	S.C.	0.64	S.C.	0.3	Thyrotoxic
5	S.C.	0.3	S.C.	0.64	S.C.	0.3	Thyrotoxic
6	S.C.	0.3	I.V.	0.64	S.C.	0.3	Control
7	S.C.	0.3	I.V.	0.64	S.C.	0.3	Control
8	S.C.	0.3	I.V.	0.64	S.C.	0.3	Control
9	S.C.	0.3	S.C.	0.64	S.C.	0.3	Control
10	S.C.	0.3	S.C.	0.64	S.C.	0.3	Control
11	I.V.	0.01 mg./min.	I.V.	0.64	I.V.	0.01 mg./min.	Control
12	I.V.	0.0096 mg./min.	I.V.	0.64	I.V.	0.0096 mg./min.	Control
13	I.V.	0.0055 mg./min.	S.C.	0.64	I.V.	0.0055 mg./min.	Control
14	I.V.	0.0063 mg./min.	S.C.	0.64	I.V.	0.0063 mg./min.	Control

Epinephrine Subcutaneously (Cases 1 to 10). In observation 1, after control levels were established, 0.3 cc. of normal saline solution was injected and ten minutes later 0.3 cc. of a 1:1000 solution of epinephrine hydrochloride was given. Both injections were subcutaneous. The blood pressure and pulse rate were determined at two minute intervals for at least thirty minutes thereafter. Observation 2 was made five to eight hours later on the same day (with the exception of case 3). After a thirty minute rest period, 2.0 cc. of normal saline solution was injected either subcutaneously or intravenously, corresponding to the route of the subsequently administered atropine. Ten minutes later 0.64 mg. of atropine sulfate was given. If given intravenously,

fifteen minutes was allowed to elapse before the subsequent subcutaneous injection of 0.3 mg. of epinephrine; if the atropine was given subcutaneously, twenty minutes was allowed to intervene. The blood pressure and pulse rate were followed at two minute intervals for at least thirty minutes after the injection of epinephrine (fig. 1 A). In both sets of observations, the severity of the subjective distress and tremor was carefully noted.

In 4 of the 10 patients observation 2 was performed in the morning and observation 1 later in the day.

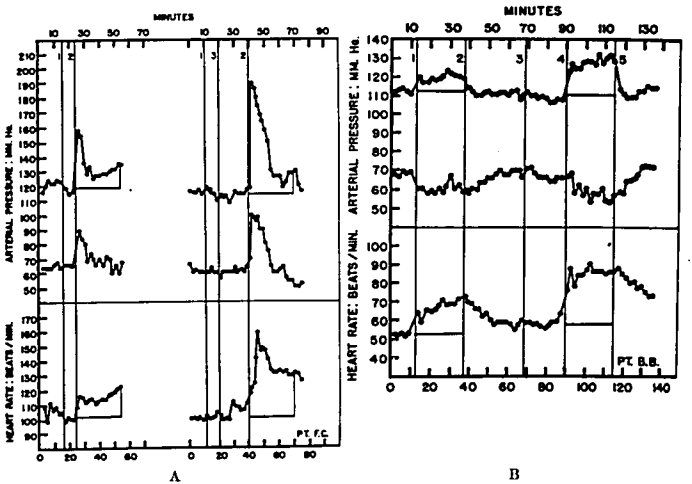

FIG. 1 A. Comparison of effect of subcutaneous administration of epinephrine before and after atropine. At 1, 0.5 cc. of normal saline was injected subcutaneously. At 2, 0.3 cc. of epinephrine hydrochloride, 1: 1000, was injected subcutaneously. At 3, 0.64 mg. of atropine sulfate was injected subcutaneously.

FIG. 1 B. Comparison of effect of intravenous administration of epinephrine before and after atropine. At 1, epinephrine hydrochloride, 1: 200,000, was introduced intravenously at a rate of 0.0063 mg. per minute. This was stopped at 2. At 3, 0.64 mg. of atropine sulfate was administered subcutaneously and from 4 to 5 the same epinephrine solution was administered at the same rate as in the period from 1 to 2.

Epinephrine Intravenously (Cases 11 to 14). A continuous intravenous drip of normal saline solution, at 30 drops per minute, was introduced into the right antecubital vein. A separate reservoir, containing a solution of 1:200,000 epinephrine hydrochloride in normal saline, was connected to the intravenous needle by means of a three-way stopcock. The dripper was carefully calibrated (22 drops per cubic centimeter) and the drip rate was made constant by the use of a long,

flat, spring clamp.‡ After control levels were obtained, the epinephrine was turned on and allowed to run in at a constant rate for about twenty-five minutes. The epinephrine drip was stopped and administration of the normal saline solution was resumed for thirty minutes. At the end of this time 0.64 mg. of atropine was administered, intravenously in 2 patients and subcutaneously in 2. Fifteen or twenty minutes later (depending upon the route of administration of atropine) the epinephrine was again turned on and allowed to run in at the same

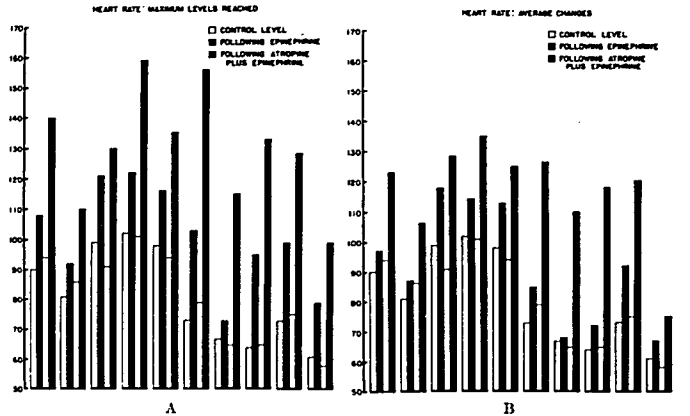

FIG. 2 A. Comparison of effect of epinephrine before and after atropine in 10 patients at maximal heart rates after injection. The first blank columns in each group represent the control level of the heart rate before, and the dotted columns represent the highest level attained after, administration of epinephrine. The second blank columns in each group represent the control level before, and the black columns represent the highest level attained after, administration of atropine and epinephrine. The first 3 patients were thyrotoxic and the last 5 were euthyroid. Numbers are 1 to 10 from left to right for correlation with table 1.

FIG. 2 B. Same as 2 A except that the dotted and black columns represent average rather than maximal changes for the thirty minute period after injection.

rate and for the same interval as described above. The blood pressure, pulse rate and drip rate were determined every two minutes (fig. 1 B).

Analysis of Results: It was thought that a consideration of the systolic pressure and heart rate in terms of both the maximal height reached and an accurate average height for the thirty minute period following injection would be more satisfactory than consideration of either value alone. All the figures obtained were plotted and subjected to planimetric analysis. The average increase per minute was determined by computing the area under the curve with the use of a com-

‡ Made by the Harvard Apparatus Co.

pensating planimeter and dividing by 30. The pre-injection level was used as a base line for the area in each case (fig. 1 A).

Two thyrotoxic patients (cases 1 and 5) were given saline solution and epinephrine as described under observation 1, and saline solution, atropine and epinephrine as described under observation 2. Before and after the administration of these agents, continuous electromyographic tracings were taken from the extensor surface of the midforearm. The total number of microvolts generated by this group of

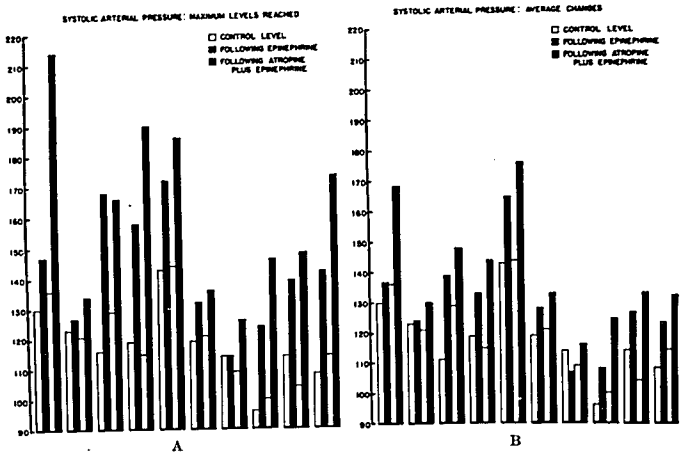

FIG. 3 A. Same as 2 A except that values are for systolic arterial pressure in millimeters of mercury.

FIG. 3 B. Same as 3 A except that dotted and black columns represent average rather than maximal changes for the thirty minute period after injection.

muscles was thus continuously recorded (2). The electromyograms were taken, examined and computed by Dr. M. A. B. Brazier of the electro-encephalographic laboratories of this hospital.

RESULTS

I. PATIENTS RECEIVING EPINEPHRINE SUBCUTANEOUSLY

A. *Heart Rate:* In all 10 patients, the *maximal* increase in heart rate above control levels was greater when the injection of epinephrine was preceded by atropine (fig. 2 A). The difference varied from *13* to *47* beats per minute with a mean of *29.5* beats per minute.

In all 10 patients the *average* increase per minute in the heart rate above control levels for the thirty minute period after the injection of epinephrine was greater when atropine was given previously (fig.

2 B). The difference varied from *11* to *45* beats per minute with a mean of *25.2* beats per minute.

B. *Systolic Arterial Pressure:* In 9 of the 10 patients, the *maximal* increase of arterial pressure above control levels was greater when the injection of epinephrine was preceded by atropine (fig. 3 A). The difference varied from *2* to *61* mm. of mercury, the mean being *22* mm. of mercury. In the other patient (case 3) the *maximal* increase of arterial pressure above control levels was smaller when the injection of epinephrine was preceded by atropine than when it was given alone. In this thyrotoxic patient (the only patient in whom more than six hours intervened between observations 1 and 2), observation 2 was made eight days after observation 1 and during this time appropriate therapy had been administered (fig. 3 A).

In 9 of the 10 patients, the *average* increase in the systolic arterial pressure above control levels for the thirty minute period following the injection of epinephrine was higher when atropine was given previously (fig. 3 B). The difference varied from *2.7* to *25.7* mm. of mercury, the mean being *10.4* mm. of mercury. In the other patient (case 3, discussed above) this did not occur.

C. *Subjective Reaction:* In the euthyroid patients, the preliminary administration of atropine seemed to intensify only slightly the symptoms produced by the injection of epinephrine. The difference was not clear enough to justify any conclusions in this group. The thyrotoxic patients were in direct contrast to the normals in this regard, since the subjective reaction of these patients to epinephrine was clearly intensified when atropine was given previously. The tremor, pounding of the heart, dyspnea and apprehension were unmistakably increased. One thyrotoxic patient (case 1) complained of tightness of the chest and precordial distress when administration of atropine preceded the epinephrine, whereas this did not occur when epinephrine alone was given.

D. *Electromyograms:* The electromyograms, taken in cases 1 and 5, revealed that the electrical activity generated by the muscles of the forearm was greater and more sustained when the epinephrine was preceded by atropine than when it was given alone (fig. 4). Simultaneous observation of the hands suggested that the increase in electrical activity corresponded to the periods of increased tremor. Ink-writer records of the heart rate, taken at the same time, confirmed the previously obtained results mentioned above.

II. PATIENTS RECEIVING EPINEPHRINE INTRAVENOUSLY

In each of the 4 patients who were given epinephrine intravenously, the responses of the blood pressure and heart rate were higher when the epinephrine was preceded by atropine than when it was given alone (fig. 1 B). The maximal difference in pulse rate varied from 6 beats per minute to 25 beats per minute, the mean being 16.2 beats per minute. The maximal levels of blood pressure likewise were greater when

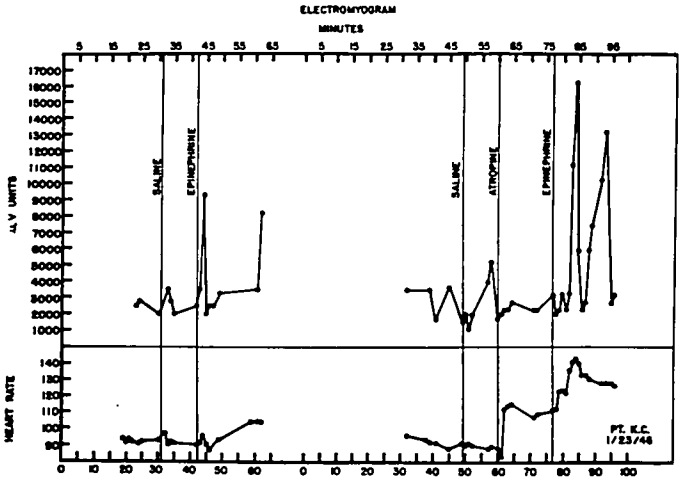

FIG. 4. Electromyograms taken after administration of epinephrine alone and after epinephrine preceded by atropine (see text).

atropine preceded the epinephrine. The difference varied from 5 mm. of mercury to 11 mm. of mercury, the mean being 8.2 mm. Since the period of injection was not precisely the same in each case, planimetric analysis would not be accurate. However, the area under both the blood pressure and heart rate curves for comparable periods was always significantly greater when the epinephrine was preceded by atropine.

Comparison of the Effect of Atropine and Scopolamine

It is believed that atropine and scopolamine differ quantitatively in their peripheral effects. Scopolamine is thought to be a stronger blocking agent on the salivary, bronchial and sweat glands and the iris and ciliary body, while atropine exerts a more pronounced effect upon the heart, bronchiolar muscle and intestine (9). It seemed worth while, therefore, to attempt to demonstrate whether scopolamine augments the heart rate and blood pressure to a lesser extent than atropine does in the presence of circulating epinephrine.

Since the comparison of the two drugs was to be a quantitative determination, it was deemed necessary to avoid the small error inherent in tablet medication. Accordingly, all the atropine and scopolamine used in the subsequently described experiments was prepared from crystalline material dried to constant weight and made up freshly on the morning of the day it was to be used.

It can be seen from the data presented in the preceding section that the intravenous administration of epinephrine at a constant rate produces a rise in heart rate and systolic arterial pressure which is greater after atropine has been administered than when epinephrine is given alone (fig. 1 B). Five additional sets of observations were obtained duplicating the conditions shown in figure 1 B with the exception that scopolamine was used in place of atropine in doses of either 0.64 or 0.43 mg. Figure 5 is representative and illustrates that in these 5 patients scopolamine did not augment the effect of epinephrine on the heart rate and arterial pressure. Of these 5 patients 2 were thyrotoxic and 3 were controls. Figure 5 shows the observations on one of the thyrotoxic patients. In each case the patient complained of dryness of the mouth and 4 of the 5 patients became distinctly somnolent.

A second type of experiment to test quantitative differences in the response of heart rate and arterial pressure was devised. After con-

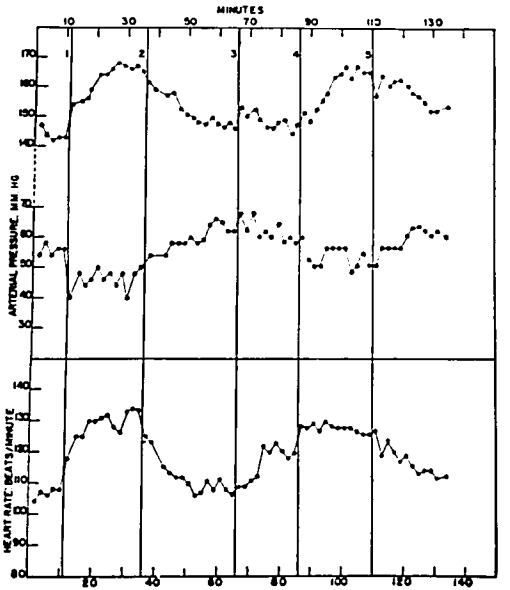

FIG. 5. Effect of epinephrine intravenously before and after scopolamine. At 1, epinephrine hydrochloride, 1: 200,000, was introduced intravenously at the rate of 0.0063 mg. per minute. This was stopped at 2. At 3, 0.64 mg. of scopolamine was administered subcutaneously and from 4 to 5 the same epinephrine solution was administered at the same rate as in the period from 1 to 2. Compare with figure 1 B.

trol levels had been obtained, epinephrine was administered intravenously at a constant rate. At the end of fifteen minutes, 0.43 mg. of atropine or scopolamine was rapidly administered intravenously in the opposite arm while the epinephrine drip was continued and was maintained for an additional fifteen minutes. The following day the same procedure was repeated on that patient at the same hour using the same set and dripper for the epinephrine and the same syringe and needle for the administration of the atropine or scopolamine. Six such sets of dual observations were obtained. In four the observations using atropine came first and in two the observations using scopolamine came first.

Figure 6 demonstrates the type of data obtained. In 4 of the 6 patients the effect of atropine on the pulse rate was greater than that of scopolamine; in the other 2 the effects of both drugs were equal. In

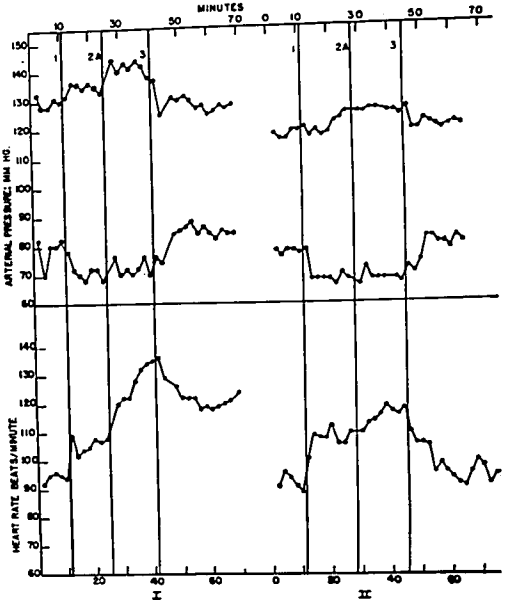

FIG. 6. Effect of atropine and scopolamine given during intravenous administration of epinephrine. At 1, epinephrine hydrochloride, 1: 200,000, was introduced intravenously at a rate of 0.0063 mg. per minute. At 2 A in I, 0.43 mg. of atropine was administered intravenously in one minute. At 2 A in II, 0.43 mg. scopolamine was given intravenously in one minute. At 3, the epinephrine drip was stopped. Observations I and II were twenty-four hours apart.

three of the six experiments, the effect of atropine on the systolic arterial pressure was greater than that of scopolamine; in the remaining three, effects were equal. In no case was the effect of scopolamine greater than that of atropine on either the heart rate or blood pressure.

DISCUSSION

The avoidance of tachycardia and hypertension even for brief periods is desirable in the patient whose heart has borne the brunt of a greatly increased metabolic load. It is suspected that auricular fibrillation is more likely to occur at higher heart rates. Similarly, it is thought likely that pulmonary congestion or frank pulmonary edema is preceded by periods of elevated arterial pressure in hypertensive and thyrotoxic patients.

Of even greater importance is the fact that the heart rate and blood pressure are the main indices of the thyrotoxic patient's condition preceding and during a surgical procedure. It is well known that the effector organs of the sympathetic nervous system are highly sensitized to the action of epinephrine in hyperthyroidism (1, 4–8, 10, 11). We believe, therefore, that it is unwise to administer any agent which will enhance the effect of epinephrine, whether it be by direct synergistic activity or by diminishing the effectiveness of those influences that buffer the epinephrine response. This is especially true at times when it is likely that the patient will secrete epinephrine, such as during the apprehension engendered in the thyrotoxic patient in the immediate preoperative period.

It may be of some clinical significance that scopolamine augments the response to epinephrine less often and to a lesser extent than atropine does. This confirms, in part, the pharmacologic opinion that scopolamine influences vagal activity on the heart less than atropine (9). It also confirms the purely clinical impression that thyrotoxic patients are less likely to overreact when scopolamine is used as premedication than when atropine is so used.

It is to be noted that no great discrepancy in the response of the heart rate and arterial pressure to epinephrine has been demonstrated between thyrotoxic and normal patients, although in general there was a slightly greater response in the former. This is due in part to the fact that the resting levels of both the systolic pressure and the heart rate initially were higher in the thyrotoxic group, so that homeostatic pressor mechanisms were brought to bear more forcefully in normal patients. Data calculated to demonstrate an alteration in the sensitivity to epinephrine attributable to hyperthyroidism would have to be collected in the same patients as they progressed from a toxic to a normal state or vice versa.

It would seem then that, in comparable doses, the difference between the influence of scopolamine and atropine is significant. If it is thought that a drying agent is essential as premedication in the thyrotoxic

patient, on the basis of the data presented above, scopolamine appears to be the drug of choice.

SUMMARY AND CONCLUSIONS

The preliminary injection of atropine sulfate, in doses commonly used clinically as preoperative medication, augments the effect of subsequently administered epinephrine hydrochloride. This is true of the thyrotoxic as well as the normal patient.

The augmented effect is evidenced by a higher and more prolonged rise in pulse rate and systolic blood pressure, and by an increase in the subjective distress and muscular tremor in the thyrotoxic patient.

The effect is independent of the route of administration used for either drug.

Inasmuch as the pulse rate and blood pressure are important criteria in evaluating the operative course of thyrotoxic patients, it seems unwise to distort these values by the administration of atropine.

Scopolamine may produce the same type of augmentation but in our series did so less often and to a smaller degree. It has the additional advantage of being effective as a drying agent in smaller doses.

ACKNOWLEDGMENT

The authors wish to acknowledge the technical assistance of Mrs. Dorothy M. Rogers.

REFERENCES

1. Asher, L., and Flack, M.: Nachweis der Wirkung eines inneren Sekretes der Schilddrüse und die Bildung desselben unter dem Einfluss der Nerven, Zentralbl. Physiol. 24: 211–213 (1910).
2. Brazier, M. A. B.: Tremors of Combat Neuroses; Comparison with Tremors of Paralysis Agitans, Delirium Tremens and Psychoneuroses of Civilian Life; Electromyographic Studies, Arch. Neurol. & Psychiat. 54: 175–180 (Sept.) 1945.
3. Cori, C. F., and Welch, A. D.: Glandular Physiology and Therapy, Chicago, Am. M. Assoc., 1942, pp. 307–326.
4. Eppinger, H.; Falta, W., and Rudinger, C.: Über die Wechselwirkungen der Drüsen mit innerer Sekretion, Ztschr. Klin. Med. 66: 1–52 (1908).
5. Eppinger, H., and Hess, L.: Zur Pathologie des Vegetativen Nervensystems, Ztschr. Klin. Med. 67: 345–351 (1908–09).
6. Goetsch, E.: Studies on Disorders of Thyroid Gland. Hypersensitiveness Test with Especial Reference to "Diffuse Adenomatosis" of Thyroid Gland, Endocrinology 4: 389–402, 1920.
7. Goetsch, E.: "Epinephrine Hypersensitiveness Test" in Diagnosis of Hyperthyroidism, Penn. Med. J. 23: 431–437 (1920).
8. Goetsch, E., and Ritzmann, A. J., Jr.: Thyroid Disorders; Suprarenal Factor in Reactions to Thyroidectomy, Arch. Surg. 29: 492–510 (Sept.) 1934.
9. Goodman, Louis, and Gilman, Alfred: The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, New York, Macmillan Co., 1941, chap. 25.
10. Lee, E. S., Jr.: Effect of Thyroxine on Sensitivity of Nictitating Membrane of Cat, Am. J. Physiol. 135: 452–459 (Jan.) 1942.
11. Levy, R. L.: Studies on Conditions of Activity in Endocrine Glands. Effect of Thyroid Secretion on Pressor Action of Adrenin, Am. J. Physiol. 41: 492 (1916)
12. Ragan, C., and Bordley, J.: Accuracy of Clinical Measurements of Arterial Blood Pressure, Bull. Johns Hopkins Hosp. 69: 504 (1941).
13. Trendelenberg, P.: Die Hormone; ihre Physiologie und Pharmakologie, Berlin, Springer, 1929, pp. 260–261.