THE INFLUENCE OF THE THYROID GLAND ON
THE RESPONSE TO ADRENALINE.

BY

D. MURRAY LYON, M.D.

(From the Department of Therapeutics, University of Edinburgh.)

At the present time a series of satisfactory tests for functional efficiency is amongst the most urgent needs of the practical physician. Unfortunately most of the tests introduced are so elaborate and require so much apparatus that they can only be performed in well equipped hospital laboratories, and are consequently lost to the general practitioner and his patients. One of the best examples of this need is in the so-called border-line cases where the diagnosis lies between a minor degree of thyroid overactivity and a neurosis. The estimation of the basal metabolic rate gives a measure of the thyroid activity, but this method of examination is confined at present to hospital practice.¹ A close relation between the state of the thyroid gland and the action of adrenaline has long been known to exist, and Goetsch has made this the basis of his test for hyperthyroidism.

In animal experiments it has been shown that removal of the thyroid gland lessens the response of the subject to a subsequent injection of adrenaline, and conversely that the administration of thyroid^{2,4,5,6} enhances the adrenaline reaction. Stimulation of the cervical sympathetic, by causing active secretion from the thyroid, produces a similar effect.⁸ In these cases the thyroid hormone is believed to sensitize the sympathetic nerve endings to the action of adrenaline. Eppinger and Hess,⁷ Barker and Sladen,⁸ and Lehmann⁹ have shown that these results hold good for man also. Goetsch¹⁰ gives as a standard a dose of 0.5 c.cm. of 1 in 1,000 adrenaline chloride subcutaneously, and notes in the patient the changes produced in the blood pressure and pulse rate. The typical positive reaction is "a rise of about 10 points in pulse or in systolic pressure or in both, together with certain clear-cut subjective and objective symptoms" (palpitation, tremor, apprehension, etc.). The merits of this reaction have been widely discussed and much adverse criticism has appeared.

Plummer¹¹ believes that thyroxin quantitatively controls the rate of cellular metabolism, but he has pointed out that the supposed relation between thyroid and adrenals can be explained on grounds involving the rate of blood flow, entirely apart from any other action. A similar position is taken up by Kendall¹² when he states that, "if viewed purely from a consideration of the physics involved, the injection of adrenaline into a subject with a normal basal metabolic rate will be necessarily different from injection of the same quantity into a subject with a metabolic rate 30 per cent. above normal." Aub¹³ also rejects the theory of specific sensitization and decides that the thyroid is not an essential factor in the action of epinephrin and that the effects of thyroxin and epinephrin are distinct and not interdependent. It is interesting to note that Marine and Lenhart³ continued to get an increase in metabolic rate after administration of adrenaline to rabbits previously deprived of the thyroid gland. Sandiford,¹⁴ who reports 46 observations in 39 patients, found no relation between the intensity of the adrenaline reaction and the condition of the thyroid; and she doubts if there is any sound physiological foundation for the belief. Other observers have found that positive reactions are frequently obtained in non-goitrous subjects. A number of physically fit, symptomless students examined by van Wagenen¹⁵ showed a positive response in 20 per cent., and Tomkins, Sturgis, and Wearn¹⁶ found 65 per cent. of positives in cases of irritable heart (in which condition the basal metabolic rate is normal¹⁷). Herring, reviewing the subject, sums up the position thus: "The specific action of the thyroid in sensitizing tissues amenable to adrenaline, though not improbable, is not yet proved."¹⁸

The present position¹⁹ of the adrenaline test appears to be that a negative finding is valuable in definitely excluding hyperthyroidism, whereas a positive result is of less significance, since it is frequently got in cases where no evidence of an overacting thyroid exists.

Details of Investigation.

The question has recently been investigated in a number of patients in the medical wards of the Edinburgh Royal Infirmary. The cases examined include four hypothyroid

patients, seven with exophthalmic goitre, three asthmatics, five diabetics, and several others who showed no obvious sign of endocrine disturbance (some fifty examinations in all). The subjects, having fasted overnight, were allowed to rest quietly with the mask adjusted for thirty to sixty minutes before the records were started. When the pulse rate and blood pressure readings had fallen to a steady level a sample of expired air was taken for the estimation of the basal metabolic rate. A subcutaneous injection of 0.5 c.cm. of a 1 in 1,000 solution of adrenaline chloride (P. D. and Co.) was then given, and thereafter the pulse and blood pressure were estimated at two-minute intervals, and the expired air was collected over successive ten-minute periods for an hour.

TABLE I.

Metabolic Rate.*		Blood Pressure.			Pulse.			Diagnosis.
Bas.	Max.	Bas.	Max.	Inc.	Bas.	Max.	Inc.	
122	143	140	160	20	104	137	33	Exophthalmic.
120	150	148	183	35	105	152	47	Exophthalmic.
120	150	142	186	44	102	148	46	Exophthalmic.
120	152	135	157	22	106	131	25	Treated myxoedema.
119	154	125	150	25	71	86	15	Neurasthenia.
118	153	135	145	11	100	132	32	Asthma.
63	72	115	120	5	78	94	16	Untreated hypothyroids.
64	123	119	132	13	57	78	21	
64	73	110	139	29	69	111	42	

Bas. = Basal; Max. = Maximum; Inc. = Increase.

* In order to facilitate comparison the Du Bois normal is taken as 100 and the figures found are given as 122 and 63 instead of the more usual + 23 and - 37.

The influence of the state of the thyroid on the character of the response to adrenaline has been investigated in two ways: (a) by comparing the reactions in different subjects, and (b) by examining the same individuals on more than one occasion.

(a) *Reactions in Different Individuals.*—When viewed as a whole, these show little relation to the activity of the thyroid as determined by the basal metabolic rate. A large cardiovascular response may be present in a patient with a low metabolism and vice versa. The majority of the subjects gave a positive response as estimated by Goetsch's criteria, and only four showed an increase of less than ten points in the blood pressure. The lack of uniformity can best be shown by a comparison of patients with approximately similar basal metabolic rates. Two such groups are recorded in Table I. It will be noticed that even in the cases of untreated hypothyroidism all the reactions save one are greater than ten points.

(b) *Reactions in the Same Subject.*—If it be true that thyroxin sensitizes the body to the action of adrenaline the effect should be evident when the amount of the thyroid hormone in the patient is varied. Table II gives the results of the examination of four subjects before and after the administration of thyroid extract. Two of the patients (1 and 2) were cases of myxoedema with very low metabolic rates; the other two suffered from asthma. Of the latter, No. 4 showed rather high basal figures, while No. 3 was

TABLE II.—Cases Given Thyroid Extract.

Case.	Date.	Metabolic Rate.		Blood Pressure.			Pulse.			Diagnosis.
		Bas.	Max.	Bas.	Max.	Inc.	Bas.	Max.	Inc.	
1	Aug. 23	64	123	119	132	13	57	78	21	Myxoedema.
	Oct. 4	106	163	120	140	20	69	91	22	
2	June 2	63	72	115	120	5	78	94	16	Myxoedema.
	July 5	120	152	135	157	22	106	131	25	
3	Aug. 22	107	135	136	150	14	98	124	25	Asthma.
	Aug. 31	118	153	135	146	11	100	132	32	
4	Aug. 25	114	144	156	203	12	108	131	23	Asthma.
	Oct. 12	142	165	192	225	33	118	148	30	

TABLE III.—Cases of Hyperthyroidism before and after Treatment.

Case.	Date.	Metabolic Rate.		Blood Pressure.			Pulse.		
		Bas.	Max.	Bas.	Max.	Inc.	Bas.	Max.	Inc.
5	Aug. 9	120	159	148	183	35	105	152	47
	Sept. 1	120	160	142	186	44	102	148	46
	Nov. 1	102	142	142	152	10	76	124	48
6	Aug. 21	122	157	140	160	20	104	137	33
	Sept. 28	112	140	122	152	30	88	122	34
7	July 31	140	199	160	191	31	120	139	19
	Aug. 30	125	160	141	182	41	95	108	13

normal. The effect of the thyroid in raising the general activity of the body is evident in the increase of basal metabolic rate, basal pulse rate, and basal systolic pressure readings, while in those observations made after the giving of thyroid extract its sensitizing effect is shown in the great increase in the pulse and pressure seen in all instances except one.

Confirmation would be expected in cases of exophthalmic goitre examined at different phases of the disease. The results shown in Table III at first sight seem contradictory. The cases were first examined shortly after admission to hospital and were re-examined when the clinical condition had improved. On the subsequent occasions the basal metabolic rates had fallen greatly and the slowing of the pulse was even more marked, the reduction in the case of the basal systolic blood pressure being less evident. In case No. 5 the reactions to adrenaline agreed very closely on two occasions when the basal metabolic rate stood at 120. On the third examination, though the basal levels were much reduced, the post-adrenaline increases in metabolic rate and in pulse rate were practically the same as before treatment. Cases 6 and 7 showed a definite reduction in metabolic response, but in both patients the post-adrenaline blood pressure rise was greater and the pulse acceleration was little affected. Such results would suggest that the thyroid controls only the basal levels, while the reaction to adrenaline depends on some other independent mechanism.

Experimental proof of the interrelationship of the thyroid and the suprarenal seems to be complete. Adrenaline stimulates the thyroid to activity, and the thyroid hormone controls the rate of activity of the body tissues, including the adrenal glands. It is also believed that the thyroid sensitizes the sympathetic nerve endings on which adrenaline acts, so that an increase in thyroid activity should lead to an increased reaction to adrenaline. The existence of such a relation is more difficult to prove in the case of man. Table I has shown that the movements of pulse and blood pressure in no way parallel the activity of the thyroid from case to case, and even when allowance is made for size, body weight, age, and sex (as is done in computing the basal metabolic rate) no better results are obtained.

The effect of an injection of a drug must depend to a great extent on the rate of its absorption, and a good deal of the difference between individual cases may be explainable on this ground. In some persons the maximum rise is produced within six minutes after injection, while in others twenty or thirty minutes elapse before the highest point is reached. This can only be explained on the basis of a wide difference in the rate at which the adrenaline reaches the tissues on which it acts. The rate of absorption is closely related to the circulation rate, being most rapid in the hyperthyroid cases (where the venous blood often looks pink and arterIALIZED) and slowest in those with deficient thyroids. The rate of absorption, then, has an extremely important influence on the result, for where the maximum occurs early it reaches a very high level, since a great deal of the adrenaline is in action at once. On the other hand, where absorption is slow only a limited quantity of adrenaline can be reaching the tissues at one time and its stimulating effect must be much less.

It is said that adrenaline acts quantitatively and that the injection of a series of similar doses produces uniform responses without fatigue. Hunt²⁰ showed that as increasing doses were given the response elicited was always a little less than was expected. This question has been reinvestigated²¹ with regard to the blood pressure, and it has been found that the relation between the quantity of adrenaline and the effect

produced is logarithmic. It has also been found that when uniform doses are given the magnitude of the response depends upon the level of the blood pressure from which the reaction started—for example, a dose of 0.2 c.cm. adrenaline given when the pressure stood at 136 gave a rise of 63, but a similar dose given at 246 produced only an increase of 18 mm. It will thus be seen that a rise of ten points in the blood pressure does not represent a uniform quantity of adrenaline under all circumstances—for example, to produce an increase of pressure from 190 to 200 requires a great deal more of the drug than to raise the level from 110 to 120. When applied to Table II this principle will have the effect of magnifying the increases actually obtained after the administration of thyroid; and in the case of Table III the apparent anomaly will diminish if not disappear, since the relatively large responses from a lower basal level are of less value than if from the original higher basal levels. Even when this allowance has been made, the differences in Table III fall far short of those in Table II, suggesting that the adrenaline sensitive mechanism still remains hypersensitive when the thyroid activity diminishes. (This might lend support to the view that the thyroid changes in exophthalmic goitre are merely secondary to a hypertonus of the sympathetic system.) If the two mechanisms are entirely independent, as Aub believes, an increase in thyroid activity would merely raise the basal levels and the adrenaline effect superimposed on these would have the same value whatever level the reaction started from. This does not fit the facts. The thyroid certainly does control the resting levels of pulse rate, metabolic rate, and systolic pressure, but it also sensitizes the tissues to the action of adrenaline.

Some of the points discussed may help to explain the comparative failure of Goetsch's reaction as a clinical test. The responses obtained from the injection of adrenaline reflect principally the tonus of the sympathetic system, which may or may not depend on the state of the thyroid. It would seem too that the criteria accepted are too low, since so many apparently normal persons give positive reactions.

Summary.

In a comparison of the metabolic and cardio-vascular responses to the injection of adrenaline in patients having similar basal metabolic rates no relationship between the reactions is obvious.

If individuals are examined on different occasions when their metabolic rates have altered, a change in the degree of response to adrenaline is noticed.

Administration of thyroid to a patient leads to an exaggeration of the reaction to adrenaline.

In cases of exophthalmic goitre a fall in basal metabolic rate is not accompanied by a very great reduction in the sensitiveness to adrenaline, and it is suggested that this depends on a persisting hypertonus of the sympathetic system.

REFERENCES.

- Meakins and Davies: *Edin. Med. Journ.*, 1922, vol. 28, p. 1. ²Marine and Lenhart: *Amer. Journ. Phys.*, 1920, vol. 54, p. 248. ³Asher and Flack: *Zeit. f. Biol.*, 1910, vol. 55, p. 83. ⁴Oswald: *Centralbl. f. Phys.*, 1915, vol. 30, p. 509. ⁵Santesson: *Skand. Arch. f. Phys.*, 1919, vol. 37, p. 195. ⁶Levy: *Amer. Journ. Phys.*, 1916, vol. 41, p. 492. ⁷Eppinger and Hess: *Vagotonia* (New York), 1915, Nervous and Mental Disease Publishing Co. ⁸Barker and Sladen: *Trans. Assoc. Amer. Phys.*, 1912, vol. 27, p. 471. ⁹Lehmann: *Zeit. f. klin. Med.*, 1914, vol. 81, p. 52. ¹⁰Goetsch: *New York State Journ. Med.*, 1918, vol. 18, p. 259. ¹¹Plummer: *Med. Rec. (N.Y.)*, 1918, vol. 94, p. 587. ¹²Kendall: *Trans. Assoc. Amer. Phys.*, 1918, vol. 33, p. 324. ¹³Aub: *Journ. Amer. Med. Assoc.*, 1922, vol. 79, p. 95. ¹⁴Sandiford: *Amer. Journ. Phys.*, 1920, vol. 51, p. 407. ¹⁵Van Wagenen: *Journ. Indust. Hyg.*, 1922, vol. 3, p. 343. ¹⁶Tomkins, Wear, and Sturgis: *Arch. Int. Med.*, 1919, vol. 24, p. 267. ¹⁷Peabody and others: *Amer. Journ. Med. Sci.*, 1921, vol. 161, p. 508. ¹⁸Herring: *Endocrinology*, 1920, vol. 4, p. 577. ¹⁹Goetsch: *Endocrinology*, 1920, vol. 4, p. 383. ²⁰Hunt, R.: *Amer. Journ. Phys.*, 1901, vol. 5, Proceed., p. 7. ²¹Lyon: Records to be published shortly.

THE French Association for the Advancement of Science will meet at Bordeaux from July 30th to August 4th, with Professor Sabrazès as president of the Section of Medicine and Surgery, and Professor Auché as president of the Section of Public Health. Further information can be obtained from the Secretariat of the Association, 28, Rue Serpente, Paris.

AN international leprosy conference will be held at Strasbourg from July 28th to 31st, when the following subjects will be discussed: (1) new statistical data, (2) etiology, (3) pathology, (4) treatment, and (5) social and individual prophylaxis. Communications should be sent before June 10th to the General Secretary, Professor Marchoux, 96, Rue Falguière, Paris.