STUDIES ON THE VELOCITY OF BLOOD FLOW

XIII. The Circulatory Response to Thyrotoxicosis[1]

By HERRMAN L. BLUMGART, SAMUEL L. GARGILL and DOROTHY ROURKE GILLIGAN

(From the Research Laboratories of the Beth Israel Hospital, The Thorndike Memorial Laboratory of the Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston)

(Received for publication January 20, 1930)

Parry in 1815 (1) originally described exophthalmic goitre as a form of heart disease, beginning the chapter on "Diseases of the Heart" with the following words: "There is one malady which I have in five cases seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed, in that connection, by medical writers. The malady to which I allude is enlargement of the thyroid gland." Ever since then the importance of cardiac damage in patients with thyrotoxicosis has impressed students of this disease.

Various aspects of the circulation in thyrotoxicosis have been studied to gain more adequate insight into the pathologic physiology of this condition so as to provide a rational basis for treatment. The minute volume output of the heart has been measured by several investigators, but information regarding the velocity of blood flow has not been hitherto available. The purpose of the present investigation was to learn the degree to which the blood flow is accelerated in thyrotoxicosis and to study the relation of such measurements to other aspects of the circulation.

[1] This investigation was aided in part by a grant from the DeLamar Mobile Research Fund of Harvard University.

RÉSUMÉ OF THE LITERATURE

Pulse rate and pulse pressure. In general, investigators have found that there is a definite, though inexact, correspondence between the elevation in the basal metabolic rate and the increase in pulse rate. Sturgis and Tompkins (2), in a study of 154 patients with thyrotoxicosis, found a fairly constant relationship between the resting pulse rate and the basal metabolism. They state that "a basal pulse rate below 90 per minute is seldom, and below 80 per minute is rarely associated with an increased metabolism." The rise in pulse rate is due, presumably, to increased metabolism for Minot and Means (3) observed that the degree of pulse elevation for a given metabolic rate was essentially the same in thyrotoxicosis and in chronic leukemia. Read (4), and Davies and Eason (5) corroborated the observations of Sturgis and Tompkins, finding, in spite of numerous exceptions, a general relation between the pulse rate and the basal metabolic rate. Davies and Eason also observed that as the basal metabolic rate increased, the pulse pressure likewise tended to increase. An increased pulse rate usually signifies an increased blood flow although blood flow may be actually diminished if a great reduction in the stroke volume occurs (6, 7). In brief, the pulse rate and the pulse pressure tend to be elevated with increase in minute volume output, but the relation is a varying one.

Vital capacity of the lungs. Rabinowitch (8) studied the vital capacity of the lungs in a series of patients with thyrotoxicosis and observed that it became lower as the basal metabolic rate increased. McKinlay (9) likewise found a reduction in the vital capacity of the lungs to below 70 per cent of the normal in a great majority of severely toxic cases of thyroid disease. He observed that the minute volume of pulmonary ventilation at rest was not related to the diminution in the vital capaciy of the lungs. Lemon and Moersch (10) compared the vital capacity of the lungs and basal metabolic rate in 85 subjects. They found a tendency toward decreased vital capacity with increased metabolic rates, but stated that there was no precise relationship between the two measurements in a given individual.

Minute volume output of the heart. Plesch (11) studied the minute volume output of the heart in one case of exophthalmic goitre, using an ingenious but rather crude gasometric method. He found that the minute volume output of the heart was 5,288 cc. as contrasted with 4,359 cc. in one normal subject. The pulse rate of the patient with exophthalmic goitre averaged 97, that of the normal subject 72 per minute, while the oxygen consumption was 6.47 cc. per kilo per minute as compared to 3.52 cc. for the normal subject. Rabinowitch and Bazin (12) studied the venous oxygen unsaturation of the arm blood in patients with thyrotoxicosis, and inferred that no significant increase occurred in the minute volume output of the heart or in the output per beat. Liljestrand and Stenström (13) carefully studied the minute volume output of the heart in ten healthy subjects and in eleven patients with exophthalmic goitre, using the nitrous oxide method of Krogh and Lindhard (30). Eight female patients with an average increase in the

basal metabolic rate of 58 per cent above the normal showed an increase of 80 per cent in the minute volume output of the heart, while three male patients with an increase in the basal metabolic rate of 66 per cent showed an increase of 100 per cent in the minute volume output of the heart. Davies, Meakins and Sands (14), and Blalock and Harrison (27) likewise observed that the minute volume output of the heart was increased roughly in proportion to the increased basal metabolic rate although an exact parallelism between the two measurements could not be traced in every instance. Similar results were obtained in several patients with exophthalmic goitre by Kininmonth (15) using the ethyl iodide method of Henderson and Haggard. Robinson (16), Liljestrand and Stenström (13), and Burwell, Smith and Neighbors (17) found the output of the heart increased to such an extent that the oxygen demands of the body were supplied without diminishing the oxygen tension of the mixed venous blood.

METHODS

The velocity of blood flow was measured by means of the radium active deposit method (18, 19, 20, 21). The active deposit was injected into the right antecubital vein, and the times of its arrival in the right chambers of the heart and in the arteries about the elbow of the left arm were recorded. The time that elapses between the injection of the active deposit into the antecubital vein and the arrival of the active deposit in the right chambers of the heart has been termed "the arm to heart time" for it is a measure of the velocity of venous blood flow from the arm to the heart. The time that elapses between the arrival of the active deposit of radium in the right chambers of the heart and its arrival in the arteries about the elbow of the arm has been called "the crude pulmonary circulation time" and provides an estimate of the velocity of blood flow through the lungs.

The venous pressure was measured according to the direct venipuncture method of Moritz and Tabora (22), and the vital capacity of the lungs by means of a Collins spirometer. The basal metabolic rate was measured with a Benedict-Roth apparatus. The tests were carried out under strictly basal conditions. The Aub-DuBois standard was used. All measurements were made in duplicate and did not differ by more than 5 per cent. The basal metabolic rate and the velocity of blood flow were measured on the same day in one-half of the cases, while in the rest the measurements were made on successive days. Particular care was taken to gain the confidence and coöperation of the patient so that the velocity of blood flow measurements could be made

under as nearly basal conditions as possible. The pulse rate was counted several times before and after each test. Whenever feasible, observations were repeated after the basal metabolic rate had returned to normal in order to study the effect of treatment.

RESULTS

Twenty-seven measurements of the pulmonary circulation time and related aspects of the circulation were made in thirteen patients. In studying the data it seemed desirable to divide the patients into two groups. The first group includes nine patients who showed no clinical evidence of circulatory insufficiency; the second group consists of four patients who showed signs of cardiovascular disease.

I. Thyrotoxic patients with no clinical evidence of cardiovascular disease

Table 1 presents the results of twenty measurements of the pulmonary circulation time and related aspects of the circulation in the nine patients of this group, all of whom had exophthalmic goitre. In all but one of the patients, (D. A.), observations were repeated when the basal metabolic rate had been lowered by treatment. The diagnoses were established by the clinical findings and by microscopic examination of the excised thyroid tissue, the results of which are given in the appended case summaries. The clinical condition of the patients varied considerably. Some individuals were very toxic and had experienced symptoms for many years, while in others the disease was less severe and of shorter duration. Six of the nine patients were females, and three patients were males. The ages of the patients varied from 18 to 45 years.

Blood. In all patients the hemoglobin and red blood cell concentration in the peripheral blood were within the limits of normal.

Pulse rate. The pulse rates before treatment were usually elevated but became normal with lowering of the basal metabolic rate. There was a general relation between the degree of elevation of the pulse rate and the increase in the basal metabolic rate. In a given case, however, the relation was not always evident. Patient W. F., for instance, with a basal metabolic rate of 35 per cent above the normal, had a pulse rate of 68 and 80 on two occasions before treatment, while

the pulse rate was 76 after subtotal thyroidectomy when the basal metabolic rate was only 13 per cent above the normal.

Venous pressure. No significant deviations from the normal were observed in the venous blood pressures before or after treatment.

Vital capacity of the lungs and respiratory minute volume. The vital capacity of the lungs was diminished in five of the nine patients in the absence of any evidence of circulatory failure. The diminution was an inconstant finding and was not related to the degree of elevation in the basal metabolic rate. With a decrease in the basal metabolic rate toward normal the vital capacity of the lungs tended to increase although this was not apparent in every instance. Before treatment when the basal metabolic rate averaged 33 per cent above normal, the average vital capacity of the lungs was 1870 cc. per square meter of body surface. After compound solution of iodine had been given, the average basal metabolic rate decreased to 22 per cent above normal, but the vital capacity of the lungs failed to increase. After operation, however, the average basal metabolic rate was one per cent above normal and the average vital capacity increased to 2010 cc. per square meter of body surface.

In a few patients the respiratory minute volume was measured while the basal metabolic rate was elevated and again following appropriate treatment. While there was slight diminution in the respiratory minute volume with a return of the basal metabolic rate to normal, the magnitude of the respiratory minute volume before treatment and its decrease after treatment bore no direct relation to the oxygen consumption.

Velocity of blood flow. The velocity of blood flow was strikingly increased, the pulmonary circulation time in some cases being the most rapid observed in any condition up to this time. As in our previous studies, the velocity of blood flow from the arm to the heart showed considerable variation, although in most patients it was definitely increased above the normal. The variability of the arm to heart circulation time was unusually great, due, probably, to the vasomotor instability of these thyrotoxic patients. The extent of the increase in the velocity of blood flow through the lungs was closely related to the extent of increase in the basal metabolic rate. This relationship was present in each individual case and is shown by the average results.

TABLE 1

Circulatory measurements and related aspects in patients with thyrotoxicosis who showed no clinical evidence of cardiovascular disease

Date	Name	Sex	Age	Clinical diagnosis	Pulse rate	Arterial pressure		Vital capacity		Circulation time			Pulmonary circulation velocity, percentage of normal	Basal metabolic rate, percentage variation from normal	Remarks
						Systolic	Diastolic	Observed	Per square meter	Arm to heart	Arm to arm	Pulmonary			
			years			*mm. Hg*	*mm. Hg*	*cc.*	*cc.*	*seconds*	*seconds*	*seconds*	*per cent*	*per cent*	
April 13, 1928	E. B.	F.	32	Thyrotoxicosis	108	140	80	2,500	1,610	3.5	7.5	4.0	270	+60	Before treatment. Lugol's solution M.X. t.i.d begun April 15, 1928, and ended April 24, 1928. Subtotal thyroidectomy April 25, 1928. Pathological diagnosis: Hyperplasia of thyroid
June 1, 1928	E. B.	F.	32		78	100	70	2,700	1,720	5.5	15.0	9.5	114	+9	
November 15, 1927	G. O.	F.	25	Exophthalmic goitre	98	110	70	2,800	1,730	4.5	8.5	4.0	270	+24	Before treatment. Lugol's solution M.X. t.i.d. begun November 15, 1927, and ended November 18, 1927. Subtotal thyroidectomy November 19, 1927. Pathological diagnosis: Hyperplasia of thyroid
March 21, 1928	G. O.	F.	25		68	105	70	3,400	2,090	10.0	30.0	20.0	54	−3	
May 17, 1928	G. O.	F.	25		66	118	75	3,300	2,000	6.0	18.0	12.0	90	±0	
January 9, 1928	D. S.	M.	45	Exophthalmic goitre	105	115	40	3,200	1,960	2.5	8.0	5.5	196	+35	Before treatment. Lugol's solution M.X. t.i.d. begun January 21, 1928, and ended February 3, 1928. Subtotal thyroidectomy February 4, 1928. Pathological diagnosis: Hyperplasia of thyroid
June 16, 1928	D. S.	M.	45		60	124	80	3,700	2,200	11.0	29.0	18.0	60	−9	
October 6, 1927	D. A.	F.	30	Exophthalmic goitre, myasthenia gravis	120	140	92	1,800	1,190	2.0	8.0	6.0	180	+33	Before treatment

November 15, 1927	M. C.	F.	23	Exophthalmic goitre	94	120	80	2,800	1,590	11.0	17.5	6.5	166	+24	Before treatment. Lugol's solution M.V. t.i.d. begun April 2, 1928 and ended April 15, 1928. Subtotal thyroidectomy April 16, 1928. Pathological diagnosis: Hyperplasia of thyroid
March 27, 1928	M. C.	F.	23		124	110	75	2,000	1,240	5.0	11.0	6.0	180	+26	
May 29, 1928	M. C.	F.	23		76	110	70	2,500	1,600	8.0	23.0	15.0	72	−13	
January 8, 1929	I. B.	M.	45	Exophthalmic goitre	92	140	80	4,200	2,700	8.0	14.0	6.0	180	+27	Before treatment. Lugol's solution M.X. t.i.d. begun January 11, 1929 and ended January 21, 1929. Right hemithyroidectomy January 22, 1929. Left hemithyroidectomy March 18, 1929. Pathological diagnosis: Hyperplasia of thyroid
May 20, 1929	I. B.	M.	45		68	130	90	4,100	2,400	10.0	21.5	11.5	94	+3	
March 6, 1928	Y. A.	F.	21	Exophthalmic goitre	94	110	70	3,200	2,010	3.0	9.5	6.5	166	+29	Before treatment. Lugol's solution M.X. t.i.d. begun March 22, 1928
March 23, 1928	Y. A.	F.	21		82	105	70	2,600	1,630	7.0	15.0	8.0	135	+20	
April 14, 1928	W. F.	M.	38	Thyrotoxicosis	68	110	60	3,600	2,320	8.0	16.5	8.5	127	+35	Before treatment. Lugol's solution M.X. t.i.d. begun April 15, 1928 and ended April 26, 1928. Subtotal thyroidectomy April 27, 1928. Path ological diagnosis: Hyperplasia of thyroid
April 24, 1928	W. F.	M.	38		80	115	70	3,400	2,260	3.0	10.5	7.5	144	+35	
June 16, 1928	W. F.	M.	38		76	90	40	3,500	2,170	8.0	19.0	11.0	98	+13	
October 7, 1927	F. R.	F.	18	Exophthalmic goitre	88	130	70	1,900	1,370	7.5	16.5	9.0	120	+11	Lugol's solution M.X. t.i.d. begun October 5, 1927 and ended October 14, 1927. Subtotal thyroidectomy October 15, 1927. Pathological diagnosis: Hyperplasia of thyroid
April 15, 1928	F. R.	F.	18		80	115	75	2,700	1,940	8.0	19.0	11.0	98	+7	
Average before treatment					99	123	74	2,960	1,870	4.9	10.8	5.9	183	+33	
Average after Lugol's solution					83	117	70	2,630	1,753	5.8	14.0	8.2	132	+22	
Average after operation					72	112	71	3,220	2,010	8.4	21.5	13.1	83	+1	
Normal average					76	120	80		2,250	6.6	17.4	10.8	100	±0	

In a previous study of fifty-eight normal persons, the arm to heart circulation time averaged 6.6 seconds, and the crude pulmonary circulation time 10.8 seconds. In these patients with thyrotoxicosis in whom the basal metabolic rate averaged 33 per cent above normal, the arm to heart circulation time averaged 4.9 seconds and the crude pulmonary circulation time 5.9 seconds. These results signify an in-

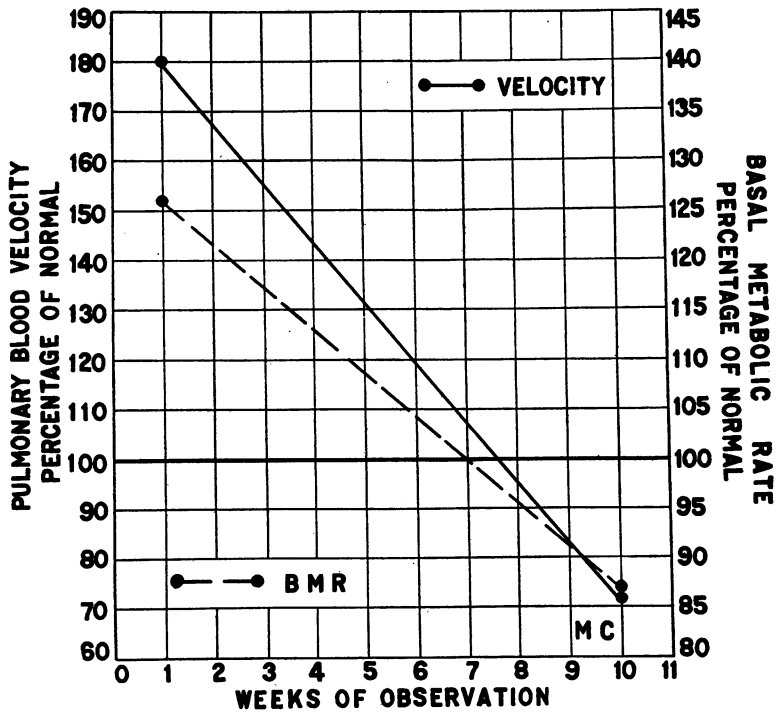

FIG. 1. RELATION OF THE VELOCITY OF BLOOD FLOW THROUGH THE LUNGS AND BASAL METABOLIC RATE IN PATIENT M. C. SUBTOTAL THYROIDECTOMY WAS PERFORMED DURING THE FOURTH WEEK OF OBSERVATION

creased velocity of blood flow from the arm to the heart of 34 per cent and an increased speed of blood flow through the lungs of 83 per cent above the average of normal.

As the basal metabolic rate became lower, the velocity of blood flow likewise approached normal. This is shown graphically in figure 1, as well as by the results in table 1. The slowing in blood flow toward normal as the basal metabolic rate was lowered by Lugol's solution

TABLE 2

Circulatory measurements and related aspects in patients with thyrotoxicosis who showed clinical evidence of cardiovascular disease

Date	Name	Sex	Age	Clinical diagnosis	Pulse rate	Arterial pressure		Vital capacity		Circulation time			Pulmonary circulation velocity, percentage of normal	Basal metabolic rate, percentage variation from normal	Remarks
						Systolic	Diastolic	Observed	Per square meter	Arm to heart	Arm to arm	Pulmonary			
			years			*mm. Hg*	*mm. Hg*	*cc.*	*cc.*	*seconds*	*seconds*	*seconds*	*per cent*	*per cent*	
January 8, 1929	L. R.	M.	36	Thyrotoxicosis, thyrotoxic heart	90	135	72	3,100	1,970	4.0	10.0	6.0	180	+33	Before treatment
February 13, 1928	M. B.	F.	61	Thyrotoxicosis	116	195	110	1,500	960	7.0	13.0	6.0	180	+50	Before treatment. Lugol's solution M.X. t.i.d. begun on February 13, 1928, and ended on February 20, 1928. Subtotal thyroidectomy on February 21, 1928. Pathological diagnosis: Toxic adenoma of thyroid
March 26, 1928	M. B.	F.	61	Hypertension	88	200	110	2,000	1,340	6.5	16.5	10.0	108	+41	
May 10, 1928	M. B.	F.	61		90	225	120	2,000	1,250	9.0	23.0	14.0	77	+28	
February 13, 1928	R. N.	F.	45	Thyrotoxicosis	94	118	65	1,700	1,080	5.0	12.0	7.0	154	+24	Lugol's solution M.X. t.i.d. begun on February 12, 1928, and ended on February 14, 1928. Subtotal thyroidectomy on February 15, 1928. Pathological diagnosis: Hyperplasia of thyroid
April 17, 1928	R. N.	F.	45	Thyrotoxic heart, auricular fibrillation	69	115	70	3,200	1,950	11.0	26.5	15.5	70	+7	
December 6, 1927	P. F.	M.	66	? Toxic adenoma, arteriosclerosis, thyrotoxic heart	88	120	80	2,500	1,690	7.5	17.0	9.5	114	+40	Before treatment
Average before operation					97			2,200	1,430	5.9	13.0	7.2	150	+37	
Average after operation					80			2,600	1,600	10.0	24.8	14.8	73	+18	
Normal average					76				2,250	6.6	17.4	10.8	100	±0	

affords additional rational basis for the preoperative administration of compound solution of iodine.

II. Patients with thyrotoxicosis and clinical evidences of cardiovascular disease

Seven measurements of the velocity of blood flow and related aspects of the circulation were made in the four patients of this group (table 2). Signs or symptoms of circulatory insufficiency had previously been present but were absent at the time of the test, although in one patient, R. N., auricular fibrillation was present at the time of the first, but not at the time of the second series of measurements. The vital capacity of the lungs was lowered in all patients, while the venous pressure was within the upper limits of normal. The velocity of blood flow through the lungs, although conspicuously increased, was slightly slower than the average velocity observed in the group of patients without cardiovascular disease but with similar basal metabolic rates. The pulse rate was generally increased in proportion to the elevation in the basal metabolic rate as in the preceding group of patients.

DISCUSSION

The work done by the heart consists mainly in expelling the blood into the aorta and into the pulmonary artery against the existing pressures, and in imparting to the blood a certain velocity. The conspicuously increased velocity of blood flow found in patients with thyrotoxicosis emphasizes the strain under which the heart labors even when the body is under basal metabolic conditions.

Certain facts assume increased significance when considered in relation to our results. The hot, flushed, salmon-colored skin, the tendency to perspire, the increased pulse pressure, the tendency to increased blood volume (23) and the diminution in the vital capacity of the lungs observed clinically suggest that considerable vasodilatation is present in thyrotoxicosis and that the functional cross sectional diameter of the peripheral and pulmonary vascular bed is increased. The relation between volume flow and velocity flow through tubes of known diameter is a simple one and is expressed by the equation

$v = \frac{a}{\pi r^2}$ where v = velocity expressed in seconds, a = volume per second and r is the radius of the tube. If other factors remain equal, an increase in the functional cross sectional area of the vascular bed would tend to diminish the speed of blood flow. The fact that the velocity of blood flow is so strikingly increased in spite of the existence of considerable vasodilatation is further evidence of the extreme strain under which the heart labors (24).

Although the second group of patients experienced dyspnoea on the slightest exertion, the velocity of blood flow was only slightly slower than that observed in similar patients (group I) without cardiovascular disease. This fact emphasizes the close interdependence of the circulatory-respiratory-metabolic mechanism. Increased tissue metabolism cannot take place unless there is a proportionate increase both in blood flow and in effective pulmonary ventilation. The observations on the velocity of blood flow in the patients of group I, in whom there was no evidence of cardiovasulcar disease, indicate the degree to which the velocity of blood flow was increased to satisfy the increased metabolic demands of the tissues. A blood flow less rapid than this in the patients of group II was evidently inadequate and was accompanied by dyspnoea on the slightest exertion. This finding is of interest for while the velocity of blood flow was slightly slower in the patients of group II than in the patients of group I, it was nevertheless much more rapid than that found in normal subjects. The question of whether a given velocity of blood flow is adequate, therefore, cannot be decided in any absolute terms but only in relation to the metabolic rate of that patient. According to this concept the term "normal velocity of blood flow" denotes the velocity of blood flow found in normal subjects with a normal basal metabolic rate.

The extremely rapid velocity of blood flow observed in patients with thyrotoxicosis affords additional information as to why such individuals experience signs and symptoms of circulatory insufficiency on but relatively slight exertion. Plummer and Boothby (25) have shown that a given amount of work by thyrotoxic patients is accompanied by a disproportionate rise in the basal metabolic rate requiring a similar disproportionate rise in ventilation and in blood flow. Rabinowitch (8) and others have shown that the vital capacity of thyrotoxic

patients is greatly diminished, thereby imposing a limitation on the degree to which the ventilation can be increased. The work of Liljestrand and Stenström (13), Bock and Field (26), Kininmonth (15), Burwell, Smith, and Neighbors (17), Means and Newburgh (29) and others indicates that the minute volume output of the heart in thyrotoxic patients at rest corresponds to that in normal individuals doing light work. This indicates that the "reserve" in the minute volume output of the heart is utilized by thyrotoxic patients even while at rest. The extremely rapid blood flow found in the present studies indicates similarly that what may be termed the "reserve" in the velocity of blood flow has been seriously encroached upon. In brief, a thyrotoxic individual experiences dyspnoea more readily than a normal one because: (1) an increased gaseous exchange is necessary; (2) a greater expenditure of energy and hence a relatively greater degree of hyperpnea is necessary to accomplish a given task; (3) the pulmonary bellows are much less efficient; (4) the "reserve" in the minute volume output has been moderately, and the "reserve" in the velocity of blood flow has been greatly encroached upon even while the patient is at rest.

The greatly increased work of the heart even under basal conditions serves to explain the frequency of circulatory insufficiency in thyrotoxicosis. Whether the frequency of cardiac damage in this condition is due partly to a specific toxic effect on the heart cannot be stated on the basis of present knowledge.

The increased velocity of blood flow in thyrotoxicosis probably occurs to meet the demands of the elevated metabolic rate and not as a result of a toxic effect on the heart. We have observed several patients with essential hypertension in whom the basal metabolic rate was elevated as high as plus 33 per cent without the clinical evidence of thyrotoxicosis. Measurements demonstrate that in these subjects the increase in the velocity of blood flow through the lungs is similar to that observed in thyrotoxic patients with equally high metabolic rates but without hypertension. The findings are in accord with certain observations on the minute volume output of the heart (14, 28). The increased burden imposed by this elevation of basal metabolic rate is of serious import to the already overworked heart and indicates the advisability of reducing the basal metabolic rate in such patients

by appropriate means. Such reduction of the basal metabolic rate while tending to lessen the amount of the cardiac work, could not be expected to affect the degree of the arterial hypertension. Similar considerations probably apply to other states such as leukemia and fever in which the metabolic rate is elevated. These observations, again demonstrate that alteration of one fundamental physiological function is accompanied by changes which tend to keep constant the various relationships within the internal environment.

SUMMARY

1. Twenty-seven series of measurements were made in thirteen patients with thyrotoxicosis in order to correlate the clinical manifestations with changes in the velocity of blood flow through the lungs, the basal metabolic rate, pulse rate, venous and arterial pressures and vital capacity of the lungs. Measurements made when the basal metabolic rate was elevated were compared with subsequent measurements when the rate was reduced.

2. There was a general but inexact relation between the degree of elevation of the pulse rate and the increase in the basal metabolic rate.

3. No significant deviations from the normal were observed in the venous blood pressure before or after treatment.

4. Diminution in the vital capacity of the lungs was an inconstant finding. With a decrease in the basal metabolic rate, the vital capacity of the lungs tended to increase.

5. The velocity of blood flow was strikingly increased so that the pulmonary circulation time was the fastest yet recorded in man. The increase in velocity of blood flow through the lungs was proportional to the degree of elevation in the basal metabolic rate. This emphasizes the strain under which the heart labors in thyrotoxicosis.

6. In nine patients with thyrotoxicosis but without circulatory failure, the basal metabolic rate averaged 33 per cent above the normal, while the velocity of blood flow through the lungs averaged 83 per cent above the normal. In four thyrotoxic patients with similar basal metabolic rates but with cardiovascular disease, the velocity of blood flow was slightly slower. The fact that the latter group of patients experienced dyspnoea on slight exertion emphasizes the close interdependence of the circulatory-respiratory-metabolic mechanism.

7. When the basal metabolic rate was lowered by the administration of compound solution of iodine or by operation, the velocity of blood flow was correspondingly slowed.

ABSTRACTS OF HISTORIES AND PHYSICAL EXAMINATIONS OF PATIENTS WITH THYROTOXICOSIS

E. B. entered the hospital because of nervousness and loss of weight. She had become increasingly nervous during the four years before admission. One year before admission she became distinctly irritable and noted an undue tendency to perspire. Six months before admission a swelling appeared in the front of the neck. During the three weeks preceding her entry to the hospital she had occasional dyspnoea and palpitation. There had been a loss of 17 lbs. in weight during the last six months. *Physical examination* showed marked nervousness; a moist, warm skin; a flushed face; symmetrical enlargement of the thyroid gland with systolic bruit over it; the heart not enlarged, with rate of 100 per minute; fine tremor of fingers and hyperactive reflexes. The blood pressure was 140 mm. Hg systolic and 80 mm. Hg diastolic. The basal metabolic rate was plus 60 per cent on April 12. Ten minims of Lugol's solution were given three times daily from April 15 to April 24. Subtotal thyroidectomy was performed on April 25. The pathological report was "Marked chronic inflammation, with marked follicular hyperplasia, and no colloid distention; hyperplasia of thyroid."

G. O'M. entered the hospital because of nervousness, fatigue and swelling of the neck. For eighteen months before admission she had noticed easy fatigability, restlessness and tremor of the hands. One year before admission she began to perspire unduly and noted a swelling at the base of the neck. She experienced palpitation on slight exertion during the two months before admission. She lost 20 lbs. within the six months preceding her entry to the hospital, although her appetite remained very good. *Physical examination* showed restlessness; quick, jerky movements; warm, moist skin; slight exophthalmos; symmetrical enlargement of the thyroid gland, with a bruit over the isthmus. Her heart was not enlarged, the rate was 94 per minute. The blood pressure was 120 mm. Hg systolic, 70 mm. Hg diastolic. The reflexes were hyperactive and there was a fine tremor of the fingers. The basal metabolic rate was plus 24, plus 22 and plus 24 per cent on October 12, November 10 and November 16, respectively. Ten minims of Lugol's solution were given three times a day from November 15 to November 18. A subtotal thyroidectomy was performed on November 19. The pathological report was—"Sections show marked chronic inflammation, with very marked follicular hyperplasia, the epithelium being columnar in type, and showing retrograde changes. There is no colloid distention; hyperplasia of thyroid."

D. S. came to the hospital because of nervousness, easy fatigability, and trembling of hands, two months in duration. In spite of increased food intake, he had

lost 15 pounds in the two months preceding his entry into the hospital. *Physical examination* showed nervousness; flushed facies; warm, moist skin; slight exophthalmos with definite stare; no thyroid gland enlargement; normal sized heart, with rate of 90 per minute. The blood pressure was 115 mm. Hg systolic and 40 mm. Hg diastolic. There was fine tremor of both hands. The basal metabolic rate was plus 40 and plus 35 per cent on December 28 and January 7, respectively. Ten minims of Lugol's solution were given three times a day from January 21 to February 3. Subtotal thyroidectomy was performed on February 4. The pathological report was "Moderate chronic inflammation with very marked follicular hyperplasia, showing retrograde changes; hyperplasia of thyroid."

D. A. had had a right hemithyroidectomy in 1915, twelve years before the present admission to the hospital. Three years previously drooping of the eyelids was first noted. Four months before admission she had to give up her work on account of increasing weakness and nervousness. Dysphagia and dysarthria gradually developed. Food seemed to lodge in her throat, and her voice became nasal in quality. Two months before admission diplopia was noted, especially on fatigue. She had lost 20 pounds during the four months preceding admission. She reentered now because of nervousness, weakness, difficulty in talking and swallowing, and drooping of the eyelids. *Physical examination* showed complete ptosis of the upper eyelids; limitation of ocular movements laterally and upward; weakness of facial muscles without atrophy; nasal quality to speech; well-healed, semi-circular scar at base of neck; small, hard mass moving with deglutition to the right of the hyoid bone; normal sized heart, with rate of 120 per minute; warm, moist skin and marked tremor of fingers. The blood pressure was 140 mm. Hg systolic and 90 mm. Hg diastolic. The basal metabolic rate was plus 23, plus 32 and plus 31 per cent on September 27, October 10 and 11, 1927, respectively. The clinical diagnosis was not only exophthalmic goitre but also myasthenia gravis. Ten minims of Lugol's solution were given three times daily from October 11 to October 23. Left hemithyroidectomy was performed on October 24. She died October 26. The pathological report was "Moderate chronic inflammation with moderate follicular hyperplasia, the epithelium being columnar in type; hyperplasia of thyroid."

M. C. entered the hospital because of swelling in her neck, palpitation, nervousness and difficult breathing. Four months before admission increased nervousness, voracious appetite and a tendency to perspire freely were noted. Six weeks before admission a swelling in the neck and tremor of the hands appeared. During the month before entry she had experienced palpitation and dyspnoea, especially on lying down. *Physical examination* showed a warm, moist skin; fine tremor of extended hands; moderate exophthalmos with bilateral lid-lag, symmetrical enlargement of thyroid gland with bruit; heart of normal size with rate of 120 per minute and a soft blowing systolic murmur over the apex. The blood pressure

was 136 mm. Hg systolic, 98 mm. Hg diastolic. The basal metabolic rate was plus 28 and plus 24 per cent on November 11 and 16, 1927, respectively. Treatment was delayed because the patient developed an upper respiratory tract infection and an acute purulent otitis media. Ten minims of Lugol's solution were given three times daily from April 2 to April 15, 1928. Subtotal thyroidectomy was done the next day. The pathological report was "Sections show marked chronic inflammation, with marked follicular hyperplasia, the epithelium being columnar in type, and no colloid distention. Parenchymatous hyperplasia of thyroid."

I. B. had suffered from nervousness, loss of weight, tremor of hands, and palpitation for one year before admission to the hospital. During the two months preceding his entry, eight to ten attacks of palpitation occurred daily. He perspired unduly and fatigued easily. *Physical examination* showed nervousness and restlessness. The skin was moist, warm and salmon-colored. There was moderate exophthalmos; an enlarged thyroid gland with a bruit and thrill over it; a normal sized heart with rate of 100 per minute; and marked tremor of fingers. The blood pressure was 148 mm. Hg systolic, 68 mm. Hg diastolic. The basal metabolic rate was plus 44, plus 22 and plus 27 per cent on January 3, 5 and 9, respectively. Ten minims of Lugol's solution were given three times a day from January 11 to January 21. Right hemithyroidectomy was performed on January 22 and left hemithyroidectomy on March 18. The pathological report was "Sections show marked follicular hyperplasia, with marked chronic inflammation. There is no colloid distention of acini. Parenchymatous hyperplasia of thyroid gland."

Y. A. entered the hospital because of increasing nervousness, perspiration and swelling in her neck. A swelling first appeared in the neck seven years before admission. For two years before admission she had been markedly nervous and had suffered from disturbed sleep, and profuse perspiration. *Physical examination* showed a nervous, restless girl with flushed, moist skin; slight exophthalmos with lid-lag; symmetrical enlargement of the thyroid gland with systolic and diastolic bruit over it; normal sized heart with rate of 90 per minute; and a coarse tremor of extended hands. The blood pressure was 120 mm. Hg systolic, 70 mm. Hg diastolic. The basal metabolic rate was plus 31 and plus 29 per cent on March 1 and 5, respectively. Ten minims of Lugol's solution were given three times daily from March 22 to April 3. Subtotal thyroidectomy was performed April 4. The pathological report was "Marked chronic inflammation, with marked follicular hyperplasia, but no colloid distention. Hyperplasia of thyroid."

W. F. entered the hospital because of nervousness and loss of weight. For one year before admission he had tired easily, had become irritable and nervous, and had developed a tremor of the hands. In spite of greatly increased food intake

he had lost 20 pounds in the three months before admission. *Physical examination* revealed a flushed, moist skin; marked tremor of extended hands; heart not enlarged with rate of 120 per minute. The blood pressure was 120 mm. Hg systolic, 60 mm. Hg diastolic. There was no exophthalmos or enlargement of the thyroid gland. The basal metabolic rate was plus 36 and plus 34 per cent on April 12 and 16, respectively. Ten minims of Lugol's solution were given three times daily from April 15 to April 26. Subtotal thyroidectomy was performed on April 27. The pathological report was "Sections show moderate follicular hyperplasia, with slight chronic inflammation. There was no colloid distention. Hyperplasia of thyroid (moderate.)"

F. R. entered the hospital because of tremor of hands and nervousness. Two years before admission undue irritability and nervousness developed and one year before admission she noted tremor of hands and voracious appetite. *Physical examination* showed trembling of lips and chin; a warm, moist skin with pigmented areas under chin and in right axilla; slight exophthalmos; a palpable thyroid gland; normal heart with rate of 90 per minute; and fine and coarse tremor of both hands. The blood pressure was 130 mm. Hg systolic, 70 mm. Hg diastolic. The basal metabolic rate was plus 35 per cent on September 20 and plus 10 per cent on October 7. Thirty minims of Lugol's solution were given daily from October 5 to October 14. Subtotal thyroidectomy was performed on October 15, 1927. The pathological report was "Marked chronic inflammation, with moderate follicular hyperplasia. Epithelium columnar in type, and there are retrograde changes in acini. Hyperplasia of thyroid."

L. R. entered the hospital because of attacks of palpitation, dyspnoea and loss of weight. One year before admission attacks of palpitation gradually increasing in severity appeared. About five months before admission he began to suffer from dyspnoea on exertion with occasional attacks of severe palpitation. *Physical examination* showed a young man with a flushed, moist, salmon-colored skin, and tremor of hands. There was no exophthalmos. The thyroid gland was uniformly enlarged. The heart showed moderate enlargement to the left, action regular, rate 85 per minute. The first sound was accentuated and a systolic murmur was heard over the apex and base. The blood pressure was 135 mm. Hg systolic and 65 mm. Hg diastolic. Electrocardiographic tracings on admission showed normal rhythm, a week later, auricular fibrillation. The basal metabolic rate was plus 68 and plus 33 per cent on December 14, 1928 and January 8, 1929, respectively. Thirty minims of Lugol's solution were given daily from January 10 to January 21. Right hemithyroidectomy was performed on January 22 and and left hemithyroidectomy on March 26, 1929. The pathological diagnosis, was "Parenchymatous hyperplasia of thyroid gland."

M. B. had suffered from nervousness, dizziness and trembling of hands for one year and marked weakness for six months. During these six months she perspired

profusely and lost 25 pounds. *Physical examination* showed flushed skin and face, moderate exophthalmos with lid-lag, symmetrical enlargement of thyroid gland and fine tremor of extended hands. The heart was moderately enlarged to the left, the rate, 110 per minute. No murmurs were heard. The peripheral vessels were sclerosed and the blood pressure was 210 mm. Hg systolic and 110 mm. Hg diastolic. There were no signs of congestive heart failure. Electrocardiographic tracings showed left ventricular predominance with slurring of R_1 and S_3. The basal metabolic rate was plus 50 per cent on February 14. Lugol's solution, ten minims, three times a day, was given from February 13 to February 21. A subtotal thyroidectomy was performed February 21. The pathological report was "Sections show marked colloid distention of acini, with slight chronic inflammation. There is no evidence of hyperplasia. Toxic adenoma of thyroid gland." On March 26 she complained of weakness and trembling of hands, the blood pressure was 200 mm. Hg systolic and 110 mm. Hg diastolic, and there was slight pitting edema of lower extremities. The lungs were clear. The basal metabolic rate was plus 41 per cent. On May 10 she felt much better, had gained 22 pounds and was no longer nervous. The blood pressure was 225 mm. Hg systolic and 120 mm. Hg diastolic. The basal metabolic rate was plus 28 per cent.

R. N. entered the hospital because of attacks of palpitation, nervousness and easy fatigability, one year in duration. She had lost about 60 pounds during the year before admission, in spite of increased food intake. *Physical examination* showed a prematurely gray-haired woman; with flushed, moist skin; moderately enlarged thyroid gland; normal sized heart with rate of 94 per minute and absolutely irregular rhythm; a pulse deficit of 12; and fine tremor of extended hands. There was no exophthalmos, lid-lag, or peripheral edema. Electrocardiogram on February 13 showed auricular fibrillation. The basal metabolic rate was plus 22 and plus 24 per cent on February 10 and 14, respectively. Lugol's solution, ten minims, three times daily, was given from February 12 to February 14. Subtotal thyroidectomy was performed February 15. The pathological report was "Moderate to marked chronic inflammation. Follicular hyperplasia is very marked and the epithelium shows retrograde changes. There is no colloid distention. Hyperplasia of thyroid."

P. F. entered the hospital because of cough, dyspnoea and edema of feet. For many years he had suffered from "asthma." Three years before admission increasing nervousness developed. One month before admission sensation of pressure over the precordium, cough, and nocturnal dyspnoea appeared. Three days before admission he noticed swelling of his feet and palpitation on the slightest exertion. In spite of increased food intake, he had lost weight steadily. *Physical examination* showed a poorly nourished, elderly white man, restless and apprehensive; with marked exophthalmos; a warm, moist skin;

palpable thyroid gland with a hard nodule in the right lobe. The heart was definitely enlarged with systolic murmur over apex, rate of 90 per minute, and absolutely irregular rhythm. Peripheral vessels were markedly sclerosed. Auscultation of lungs showed prolonged expiratory phase accompanied by musical squeaks. There was pitting edema of both legs up to the knees. The blood pressure was 120 mm. Hg systolic and 80 mm. Hg diastolic. With full doses of digitalis, the edema disappeared and normal sinus rhythm was restored by the administration of quinidine sulphate. The basal metabolic rate was plus 29 and plus 40 per cent on November 5 and December 3, respectively. Ten minims of Lugol's solution were given three times daily from December 14 to December 22, 1927. Right hemithyroidectomy was performed December 23, 1927 and left hemithyroidectomy on February 9, 1928. The pathological report was "Sections show moderate chronic inflammation but marked follicular hyperplasia with columnar epithelium, showing retrograde changes. No colloid distention seen. Hyperplasia of thyroid."

BIBLIOGRAPHY

1. Parry, C. H., Vol. II, Page 111. London, 1825. Collections from the Unpublished Medical Writings of the late Caleb Hillier Parry.
2. Sturgis, C. C. and Tompkins, E. H., Arch. Int. Med., 1920, xxvi, 467. A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism.
3. Minot, G. R. and Means, J. H., Arch. Int. Med., 1924, xxxiii, 576. The Metabolism-Pulse Ratio in Exophthalmic Goiter and in Leukemia.
4. Read, J. M., Arch. Int. Med., 1924, xxxiv, 553. Basal Pulse Rate and Pulse Pressure Changes Accompanying Variations in the Basal Metabolic Rate.
5. Davies, H. W. and Eason, J., Quart. J. Med., 1924, xviii, 36. The Relation between the Basal Metabolic Rate and the Pulse-Pressure in Conditions of Disturbed Thyroid Function.
6. Meakins, J., Dautrebande, L. and Fetter, W. J., Heart, 1923, x, 153. The Influence of Circulatory Disturbances on the Gaseous Exchange of the Blood. IV. The Blood Gases and Circulation Rate in Cases of Mitral Stenosis.
7. Barcroft, J., Bock, A. V. and Roughton, F. J., Heart, 1922, ix, 7. Observations on the Circulation and Respiration in a Case of Paroxysmal Tachycardia.
8. Rabinowitch, I. M., Arch. Int. Med., 1923, xxxi, 910. The Vital Capacity in Hyperthyroidism with a Study of the Influence of Posture.
9. McKinlay, C. A., Arch. Int. Med. 1924, xxxiv, 168. The Vital Capacity of the Lungs and Its Significance in Hyperthyroidism.
10. Lemon, W. S. and Moersch, H. J., Arch. Int. Med., 1924, xxxiii, 130. Basal Metabolism and Vital Capacity.

11. Plesch, J., Ztschr. f. exper. Path. u. Therap., 1909, vi, 380. Hämodynamische Studien.
12. Rabinowitch, I. M. and Bazin, E. V., Arch. Int. Med., 1926; xxxviii, 566. The Output of the Heart per Beat in Hyperthyroidism.
13. Liljestrand, G. and Stenström, N., Acta Med. Scandinav,. 1925, lxiii, 99. Clinical Studies on the Work of the Heart during Rest. I. Blood Flow and Blood Pressure in Exophthalmic Goiter.
14. Davies, H. W., Meakins, J. and Sands, J., Heart, 1924, xi, 299. The Influence of Circulatory Disturbances on the Gaseous Exchange of the Blood. V. The Blood Gases and Circulation Rate in Hyperthyroidism.
15. Kininmonth, J. G., Quart. J. Med., 1928, xxi, 277. The Circulation Rate in Some Pathological States with Observations on the Effect of Digitalis.
16. Robinson, G. C., J. Am. Med. Assoc., 1926, lxxxvii, 314. The Measurement of the Cardiac Output in Man and Its Variations.
17. Burwell, C. S., Smith, W. C. and Neighbors, DeW., Am. J. Med. Sci., 1929, clxxviii, 157. The Output of the Heart in Thyrotoxicosis, with the Report of a Case of Thyrotoxicosis Combined with Primary Pernicious Anemia.
18. Blumgart, H. L. and Yens, O. C., J. Clin. Invest., 1927, iv, 1. Studies on the Velocity of Blood Flow. I. The Method Utilized.
19. Blumgart, H. L. and Weiss, S., J. Clin. Invest., 1927, iv, 15. Studies on the Velocity of Blood Flow. II. The Velocity of Blood Flow in Normal Resting Individuals, and a Critique of the Method Used.
20. Blumgart, H. L., and Weiss, S., J. Clin. Invest., 1927, iv, 389. Studies on the Velocity of Blood Flow. VI. The Method of Collecting the Active Deposit of Radium and Its Preparation for Intravenous Injection.
21. Blumgart, H. L. and Weiss, S., J. Clin. Invest., 1927, iv, 399. Studies on the Velocity of Blood Flow. VII. The Pulmonary Circulation Time in Normal Resting Individuals.
22. Moritz, F. and Tabora, D. V., Deutsch. Arch. f. klin. Med., 1910, xcviii, 475. Ueber eine Methode, beim Menschen den Druck in Oberflächlichen Venen exakt zu bestimmen.
23. Thompson, W. O., J. Clin. Invest., 1926, ii, 477. Studies in Blood Volume. I. The Blood Volume in Myxedema with a Comparison of Plasma Volume Changes in Myxedema and Cardiac Edema.
24. Evans, C. L., J. Physiol., 1919, lii, 6. The Velocity Factor in Cardiac Work.
25. Plummer, H. S. and Boothby, W. M., Am. J. Physiol., 1922, lxiii, 406. The Cost of Work in Exophthalmic Goiter.
26. Bock, A. V. and Field, H., Jr., Quoted by Means, J. H., Endocrinology, 1925, ix, 192. Circulatory Diseases in Diseases of Glands of Internal Secretion.
27. Blalock, A. and Harrison, T. R., Surg. Gyn. Obst., 1927, xliv, 617. Study Number Four on the Regulation of Circulation. The Effects of Thyroidectomy and Thyroid Feeding on the Cardiac Output.

28. Liljestrand, G. and Stenström, N., Acta. Med. Scandinav., 1925, lxiii, 142. Clinical Studies on the Work of the Heart during Rest. III. Blood Flow in Cases of Increased Arterial Blood Pressure with Observations on the Influence of Pregnancy on the Blood Flow.
29. Means, J. H. and Newburgh, L. H., Tr. Ass. Am. Phys., 1915, xxx, 51. Studies of the Blood Flow by the Method of Krogh and Lindhard.
30. Krogh, A. and Lindhard, J., Skand. Archiv. f. Physiol., 1912, xxvii, 100. Measurements of the Blood Flow Through the Lungs of Man.