

## STUDIES ON THE VELOCITY OF BLOOD FLOW

### XIV. THE CIRCULATION IN MYXEDEMA WITH A COMPARISON OF THE VELOCITY OF BLOOD FLOW IN MYXEDEMA AND THYROTOXICOSIS<sup>1</sup>

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The clinical aspects of the circulation in myxedema have aroused widespread interest, but knowledge of the pathologic physiology of the blood flow in this condition is meagre. The present study undertakes the correlation of the clinical manifestations of myxedema with changes in the velocity of blood flow, basal metabolic rate, pulse rate, plasma volume, venous and arterial pressures, respiratory minute volume and vital capacity of the lungs. The same methods were employed as in the preceding study of thyrotoxicosis (1).

#### RESULTS

Sixteen series of measurements were made in seven consecutive patients with the classical clinical manifestations of spontaneously occurring myxedema (table 1). In each patient measurements made when the basal metabolic rate was low were compared with subsequent measurements when the basal metabolic rate had been elevated to normal by appropriate doses of desiccated thyroid gland by mouth. The clinical findings in the patients are summarized in the appended abstracts. All subjects were women between the ages of 45 and 58 years, except subject E. Sa. who was 18 years old. The tendency of myxedema to occur predominantly in women is well recognized.

*Blood.* "Secondary" anemia was observed on examination of the

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TABLE 1

Circulatory measurements and related aspects in patients with myxedema

Date	Name	Sex	Age years	Hemoglobin per cent	Red blood cells mil- lions per cu. mm.	Plasma volume per kilo cc.	Pulse rate	Arterial pressure		Vital capacity		Circulation time			Pulmonary velocity, percentage of normal	Basal metabolic rate, percentage variation from normal	Treatment
								Systolic mm. Hg	Diastolic mm. Hg	Observed cc.	Per square meter	Arm to heart sec- onds	Arm to arm sec- onds	Pulmonary sec- onds			
December 5, 1927	E. St.	F.	50	66	64	100	60	2,800	1,660	12.5	38.5	26.0	42	-22	Received a total of 11.8 grams desiccated thyroid from December 6, 1927 to December 28, 1927		
December 28, 1927	E. St.	F.	50	67	88	100	60	2,600	1,560	10.0	20.0	10.0	108	+1			
January 18, 1928	E. St.	F.	50	72	63	100	65	2,650	1,600	14.5	28.0	13.5	80	-13			
March 14, 1928	M. K.	F.	58	70	39.9	69	130	2,450	1,600	4.4	5.0	29.0	24.0	45		-18	
March 26, 1928	M. K.	F.	58	60	48.8	120	115	1,800	1,230	5.6	4.0	11.0	7.0	154		+6	
February 22, 1928	M. G.	F.	53	73	3.4	60	140	2,600	1,580	2.9	10.0	30.0	20.0	54		-25	
March 6, 1928	M. G.	F.	53	87	30.5	84	135	2,500	1,550	3.8	11.0	21.5	10.5	103	-3	Received a total of 12.0 grams desiccated thyroid from February 24, 1928 to March 6, 1928	
October 4, 1928	R. F.	F.	54	74	38.0	56	120	2,100	1,220	2.6	8.0	25.0	17.0	64	-24	Received a total of 12.8 grams desiccated thyroid from October 4, 1928 to October 26, 1928	
October 26, 1928	R. F.	F.	54	79	5.0	100	130	1,850	1,100	3.6	11.0	17.5	6.5	166	+14		
February 20, 1929	S. M.	F.	48	75	4.0	62	125	2,850	1,590	2.7	12.0	27.0	15.0	72	-21	Received a total of 11.3 grams desiccated thyroid from February 21, 1929 to March 14, 1929	
March 15, 1929	S. M.	F.	48	74	3.9	82	130	2,800	1,560	3.1	9.0	18.0	9.0	120	-1		
March 27, 1928	M. M.	F.	45	80	28.2	66	120	2,200	1,300	2.2	7.5	22.5	15.0	72	-33	Received a total of 16.4 grams desiccated thyroid from March 28, 1928 to April 16, 1928	
April 16, 1928	M. M.	F.	45	86	32.5	90	120	2,500	1,530	3.8	6.0	12.0	6.0	180	+0		
April 24, 1928	M. M.	F.	45	73	112	125	80	2,300	1,420	3.7	5.0	13.0	8.0	135	+12		
March 6, 1928	E. Sa.	F.	18	88	4.4	76	100	3,000	1,660	4.3	10.0	23.0	13.0	83	-23		
March 26, 1928	E. Sa.	F.	18	88	3.9	87	110	2,700	1,540	4.5	3.5	11.5	8.0	135	-2		
March 26, 1928	E. Sa.	F.	18	88	3.9	87	110	2,700	1,540	4.5	3.5	11.5	8.0	135	-2		
Average before treatment				75	4.0	34.1	65	119	77	2,570	1,510	3.2	9.6	27.9	18.6	58	-24
Average after treatment				77	4.0	37.6	93	120	77	2,390	1,440	4.1	7.8	15.9	8.1	133	+2
Average normal				100	4.5	50.0	76	120	80	2,000	3.7	6.6	17.4	10.8	100	+0	

blood of every patient. No significant change in the degree of anemia was noted in the relatively short time that intervened between the blood flow measurements before and after thyroid treatment. The occurrence of anemia in myxedematous patients and its tendency to disappear with thyroid therapy have been noted by Emery (2) and others. Our patients were not studied over a sufficient length of time to observe a return of the blood to normal. The dilution of the blood with the increase in plasma volume which occurred following thyroid medication evidently obscured any slight increase in the absolute number of red blood cells. This is particularly evident in patient M. K. (table 1).

The plasma volume was measured both before and after treatment with thyroid extract by the brilliant vital red method used by Thompson (3). Our findings agree in general with those of Thompson who found that the plasma volume per kilogram of body weight is low in myxedema and that a significant increase occurs on administration of thyroid gland. The average plasma volume per kilo of the 7 cases before treatment was 34.1 cc. compared with 37.6 cc. after treatment. A parallelism between the changes in basal metabolic rate and plasma volume was not observed always; indeed the plasma volume per kilo decreased or remained unchanged in two of seven patients after administration of thyroid gland.

*Pulse rate and pulse pressure.* The pulse rate was low in the patients with myxedema and bore a general relation to the basal metabolic rate although an exact parallelism was not present in each case. The pulse rate averaged 65 per minute before treatment compared with an average of 93 following adequate thyroid extract therapy. Likewise, the pulse pressure was small when the basal metabolic rate was low and tended to increase somewhat after treatment. These observations are similar to those of Davies and Eason (4) and to those of Willius and Haines (5) who noted an average increase in the pulse pressure from 36 mm. mercury before treatment to 45 mm. after treatment.

*Venous pressure.* The venous pressure was within the limits of normal in all our patients, a fact which is in accord with the absence of clinical manifestations of congestive failure.

*Vital capacity of the lungs.* In all subjects, the vital capacity of the

lungs was strikingly diminished in the absence of any signs of congestive failure and did not show a significant change following treatment. We are unable to explain this phenomenon. The extent of diminution in the vital capacity was not closely related to the degree of lowering in the basal metabolic rate.

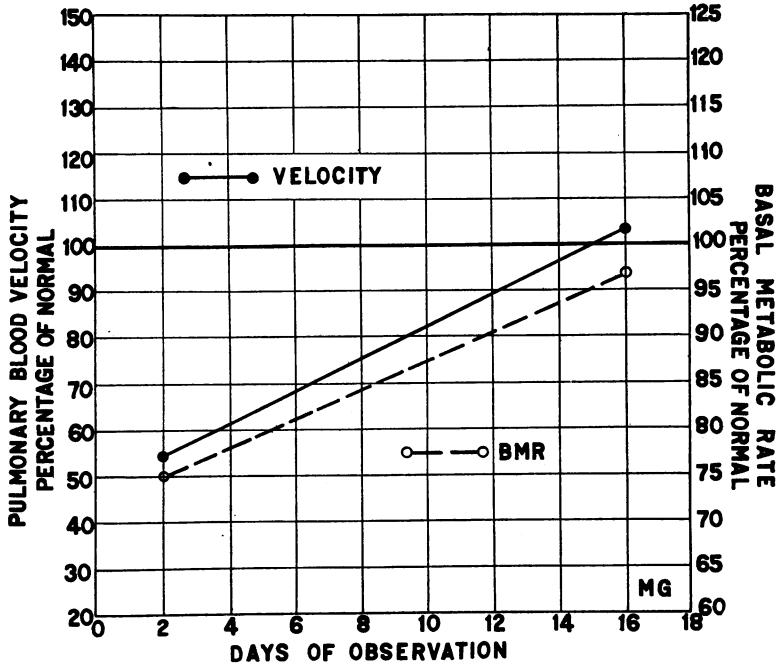


FIG. 1. THE RELATION BETWEEN PERCENTAGE VARIATIONS IN THE BASAL METABOLIC RATE AND THE VELOCITY OF BLOOD FLOW THROUGH THE LUNGS IN PATIENT M. G. BEFORE TREATMENT AND AFTER TREATMENT

The circles (○) denote observations of the basal metabolic rate, the solid dots (●), observations on the pulmonary velocity of blood flow.

*Respiratory minute volume.* The respiratory minute volume was conspicuously decreased before treatment and always rose significantly as the basal metabolic rate increased. The average respiratory minute volume per square meter of body surface before treatment was 3.2 liters compared with 4.1 liters after treatment.

*The velocity of blood flow.* The velocity of blood flow was strikingly

slow in each of the seven cases of myxedema. This was evident in both the arm to heart blood flow (the arm to heart circulation time) and the blood flow through the lungs (the pulmonary circulation time). As has been observed in all preceding studies (6, 7, 8), the arm to heart circulation time shows considerable variation because of the relatively great spontaneous fluctuations in the arm blood flow. The degree of slowing in the blood flow through the lungs corresponded closely with the degree to which the metabolic rate was lowered. After taking adequate amounts of desiccated thyroid gland by mouth, the rise in the metabolic rate and the increase in the velocity of blood flow to normal took place simultaneously and closely paralleled each other.

These findings are illustrated by the results in patient, M. G. (fig. 1). Before treatment, the basal metabolic rate was 25 per cent below the average normal, and the pulmonary circulation time was 20 seconds, denoting a slowing of the blood flow to but 54 per cent of the average normal speed. The close correspondence between changes in the velocity of blood flow and basal metabolic rate is shown by the measurements after 14 days of treatment, when the basal metabolic rate and velocity of blood flow had both returned to within 3 per cent of the average normal values.

A similar relation was observed in the measurements in patient E. S. (fig. 2). The first measurements were made before treatment when the basal metabolic rate was 22 per cent below the average normal, while the second series of tests was made after the patient had received dried thyroid gland and the basal metabolic rate had risen to 1 per cent above the average normal. Treatment was then discontinued and a third series of observations was made when the basal metabolic rate was minus 15 per cent.

The slowing of the blood flow in myxedema was not entirely unexpected but the degree of slowing was striking, being almost as great as that observed in patients with rheumatic valvular heart disease and auricular fibrillation, who had previously suffered from severe circulatory decompensation and showed symptoms or signs of congestive failure at the time of the test (7). The fact that the myxedematous patients showed no evidence of circulatory insufficiency with a speed of blood flow approximately the same as that of the latter group again emphasizes the fact that the question of whether a given speed of blood

flow is adequate can be decided only in relation to the metabolic needs of the tissues (1).

None of the myxedematous patients showed evidence of cardiovascular disease. Zondek (9), Assmann (10), Fahr (11) and others have described a form of heart failure characteristic of myxedema which

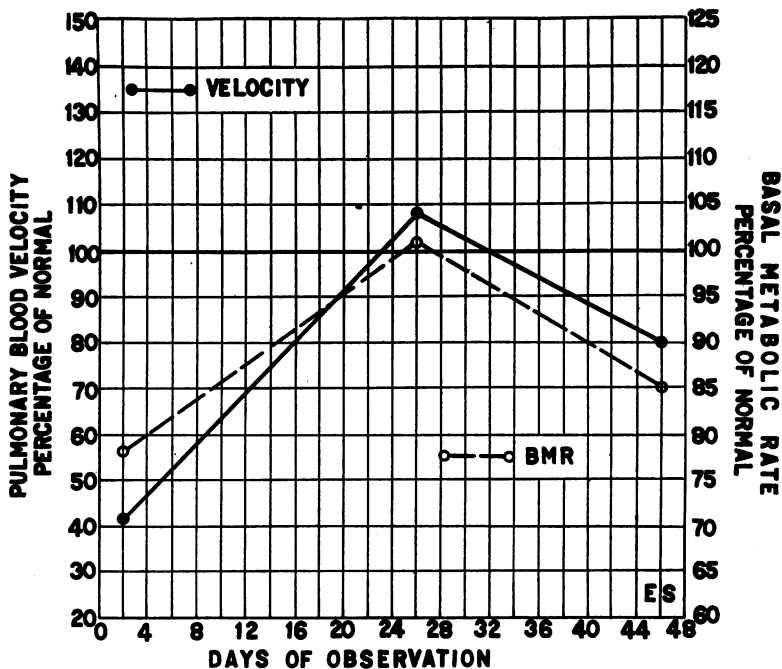


FIG. 2. THE RELATION BETWEEN PERCENTAGE VARIATIONS IN THE BASAL METABOLIC RATE AND THE VELOCITY OF BLOOD FLOW THROUGH THE LUNGS IN PATIENT E.S.

Desiccated thyroid gland was given during the first 24 days of observation. The third pair of observations was made after thyroid medication had been discontinued. The circles denote observations of the basal metabolic rate, the solid dots, observations of the velocity of blood flow through the lungs.

is alleviated only by thyroid therapy. On the other hand, Means, White and Krantz (12) in a study of 48 patients with myxedema encountered but one such case. Willius and Haines (5) in 162 cases found no evidence of heart failure or organic cardiovascular disease that

could be attributed to the presence of myxedema, and Christian (13) similarly states he has never observed the condition.

More numerous examples of the opposite course of events are available, namely, thyroid therapy precipitating circulatory insufficiency rather than alleviating it. Swan (14) has reported the case of a patient with myxedema in whom fibrillation of the auricles appeared whenever thyroid substance was administered, the heart action returning to normal whenever the drug was discontinued. Read (15), and Means, White and Krantz (12) have reported cases in which the administration of thyroid substance caused attacks of angina pectoris; and Sturgis and Whiting (16), and Pratt and Morton (17) observed cases in which at each attempt to give thyroid gland, the signs of congestive failure appeared. Christian (18) has laid particular emphasis on the danger of increasing the heart action of certain myxedematous patients by thyroid gland medication.

The results of our studies offer a rational explanation for these clinical manifestations of cardiac insufficiency following thyroid gland therapy. The great increase in blood velocity that occurs when the metabolic rate is raised to normal necessitates a conspicuously increased amount of work by the heart. Because of this and because the metabolic needs of the myocardium have risen along with those of the rest of the body, the blood supply to the heart must be increased. With the frequent occurrence of hypertension and arteriosclerotic narrowing of the coronary vessels noted by Fishberg (19) and others in cases of myxedema, the necessity for cautious administration of thyroid substance and the frequent advisability of previous digitalization is apparent.

*A comparison of changes in the pulse rate, in the basal metabolic rate, and in velocity of blood flow in myxedema and thyrotoxicosis.* In this and the preceding communication (1), attention has been directed to the relation between the clinical findings and the measurements of the velocity of blood flow and related aspects of circulation. In the following more general treatment of the data, the relation between changes in the velocity of blood flow, in the pulse rate and in the basal metabolic rate in myxedema and thyrotoxicosis will be compared.

In figures 3, 4 and 5 each dot represents an observation in a patient either before or after treatment. The results that approach normal

values represent findings in thyrotoxic patients after thyroidectomy or in myxedematous patients after thyroid substance had been administered.

*The relation between the basal metabolic rate and the pulse rate.* Figure 3 shows the relation between the pulse rate and the basal metabolic

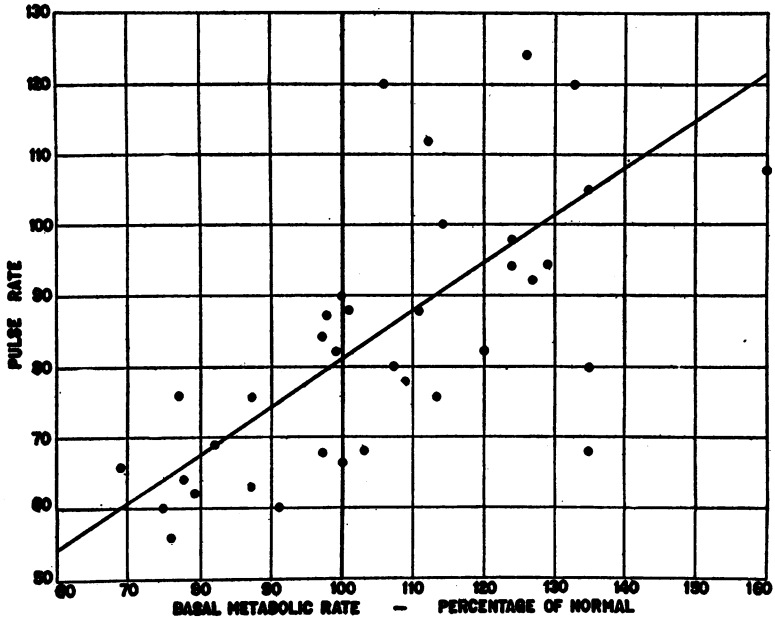


FIG. 3. THE RELATION BETWEEN THE PULSE RATE AND THE BASAL METABOLIC RATE IN PATIENTS WITH MYXEDEMA AND THYROTOXICOSIS

The observations that approach normal in this and the following figures represent findings in thyrotoxic patients after thyroidectomy or in myxedematous patients after thyroid substance had been administered.

rate in patients with myxedema or thyrotoxicosis both before and after treatment. While a general correlation is apparent, the variations of individual measurements are considerable. A similar relationship between the basal metabolic rate and the pulse rate has been noted by Sturgis and Tompkins (20) in patients with thyrotoxicosis and by Minot and Means (21) in patients with chronic leukemia. The observed variations are probably due to the fact that in order to increase



the minute volume output of the heart to meet increased metabolic demands both the stroke volume and the number of beats per minute are increased but in varying proportion in different patients. Similar variations in response can be observed in normal persons performing a standard exercise test (22).

*The relation between the pulse rate and the velocity of blood flow through the lungs.* . The relation between the velocity of blood flow through the lungs and the pulse rate (fig. 4) shows considerable variation, but is

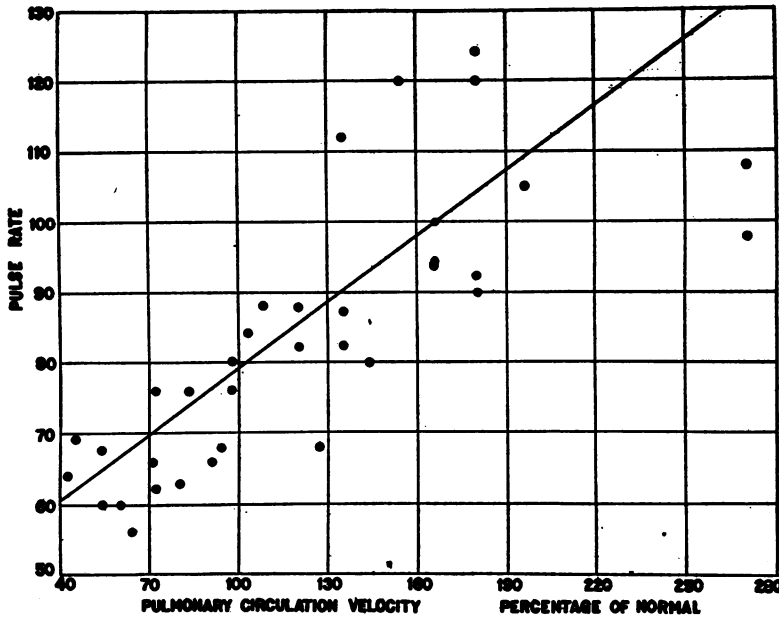


FIG. 4. THE RELATION BETWEEN THE PULSE RATE AND PERCENTAGE VARIATIONS IN THE VELOCITY OF BLOOD FLOW THROUGH THE LUNGS

closer than that between the basal metabolic rate and the pulse rate. This is in accord with what occurs in normal subjects (6). Of 58 normal subjects studied, the ventricular rate was above 90 per minute in 10, while it was below 70 in 8. The ventricular rate of the former group averaged 97 per minute and the pulmonary blood velocity averaged 29 per cent above the average normal, while the ventricular rate of the latter group averaged 65 per minute and the pulmonary blood velocity was 4 per cent below the average normal.

*The relation between the basal metabolic rate and the velocity of blood flow through the lungs.* The relation between the basal metabolic rate and the velocity of blood flow through the lungs is close and shows relatively few variations (fig. 5). This close parallelism between velocity of blood flow and metabolism is further evidence that the velocity of blood flow is a fundamental characteristic of the circulation. Comparison of the relation between the velocity of blood flow and the

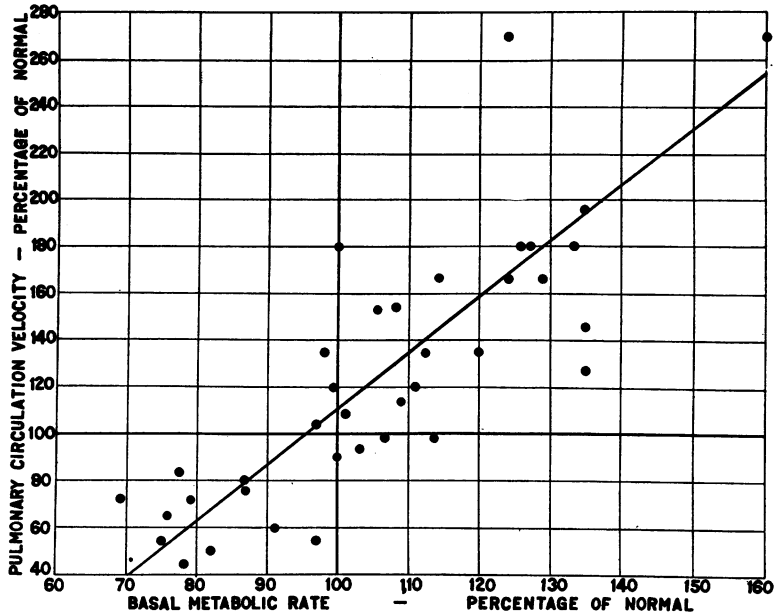


FIG. 5. THE RELATION BETWEEN PERCENTAGE VARIATIONS IN THE PULMONARY BLOOD VELOCITY AND BASAL METABOLIC RATE IN PATIENTS WITH MYXEDEMA AND THYROTOXICOSIS

basal metabolic rate in myxedema and thyrotoxicosis affords additional evidence that the increased velocity of blood flow through the lungs in thyrotoxicosis is due to the elevated metabolism rather than to a specific toxic effect on the heart. The relation between the basal metabolic rate and the velocity of blood flow is a simple linear one. (See fig. 5.) If the mean increase in the velocity of blood flow in thyrotoxicosis were due to a specific toxic effect, the line representing

the relation between the velocity of blood flow and basal metabolic rate would assume a different direction from that for myxedema. The fact that the slope is a continuous one is indirect evidence that the increased blood velocity in thyrotoxicosis is due to the increased basal metabolic rate.

It should be noted that a given percentage increase or decrease in the basal metabolic rate is accompanied by a far greater percentage change in the velocity of blood flow. This finding is in accord with observations on the relation between the minute volume output of the heart and the basal metabolism in myxedema and thyrotoxicosis (23, 24, 25, 26). This does not necessarily mean that there is a disproportionately increased velocity of blood flow in thyrotoxicosis, or a disproportionate decrease in myxedema, for the comparison involves two different phenomena which are expressed in totally dissimilar units. The results demonstrate, however, the close interrelation between the two fundamental physiological characteristics, blood flow and metabolism, and throw additional light on the degree, manner, and results of changes in the circulation associated with increased and decreased metabolic rates.

#### SUMMARY

1. Sixteen series of measurements were made in 7 patients with myxedema in order to correlate the clinical manifestations with changes in the velocity of blood flow, basal metabolic rate, pulse rate, plasma volume, venous and arterial pressures, respiratory minute volume and vital capacity of the lungs.

2. In each patient measurements when the basal metabolic rate was low were compared with subsequent measurements when the basal metabolic rate had been elevated to normal by appropriate doses of thyroid gland by mouth.

3. The plasma volume per kilogram of body weight was low and tended to increase on administration of thyroid gland.

4. The pulse rate was low and bore a rough relationship to the basal metabolic rate. As the metabolism rose the pulse rate approached normal.

5. The venous pressure was within the limits of normal in all 7 patients.

6. The vital capacity of the lungs was strikingly diminished in all subjects in the absence of any signs of congestive heart failure and did not show significant change following treatment. The extent of diminution in the vital capacity was not closely related to the degree of lowering in the basal metabolic rate.

7. The respiratory minute volume was decreased before treatment and always rose significantly as the basal metabolic rate increased.

8. The velocity of blood flow was strikingly slow in every subject and corresponded closely with the degree to which the metabolic rate was lowered. After taking thyroid gland by mouth, the rise in the metabolic rate and the increase in the velocity of blood flow to normal took place simultaneously and closely paralleled each other.

9. The slowing of blood flow in myxedema was almost as great as that observed in patients with rheumatic valvular heart disease with auricular fibrillation and symptoms and signs of congestive failure. None of the myxedematous patients showed clinical evidences of cardiovascular disease.

10. The great increase in velocity of blood flow and consequent increased cardiac work that occurs when the basal metabolic rate is raised to normal affords a rational explanation of the clinical manifestations of cardiac insufficiency which occur not infrequently following thyroid gland therapy in myxedema.

11. The changes in the pulse rate, basal metabolic rate and velocity of blood flow in myxedema are compared to those previously reported in thyrotoxicosis. The comparison indicates that the increased velocity of blood flow in thyrotoxicosis is due to the increased basal metabolic rate rather than to a specific toxic effect on the heart.

12. The findings emphasize the close interrelation between blood flow and metabolism and throw additional light on the degree, manner, and results of changes in the circulation associated with increased and decreased metabolic rates.

#### ABSTRACTS OF HISTORIES AND PHYSICAL EXAMINATIONS OF PATIENTS WITH MYXEDEMA

E. St. entered the hospital because of weakness. For two years before admission she noted that she thought and acted in a much more retarded manner than formerly. She had gained considerable weight, and her hair had become dry and brittle. One

year before admission, hearing became impaired and the voice became husky. She began to be very sensitive to cold, and required much clothing even in the warmest weather. On *physical examination* the complexion was pasty, speech thick and slow, the hair sparse and dry, the skin dry, scaly, thickened, the conjunctivae and mucous membranes pale, and the tongue thick and large. The heart was not enlarged. The ventricular rate was 60 per minute, the blood pressure 100 mm. Hg systolic and 60 mm. Hg diastolic. The basal metabolic rate was minus 24 per cent and minus 22 per cent on the 3rd and 6th of December, respectively. Thyroid gland medication was given from December 6 to December 28, 1927. During this period she received a total of 11.8 grams of desiccated thyroid gland. The basal metabolic rate on December 29 was plus 1 per cent.

M. K. had suffered from increasing weakness and easy fatigability for one year. Ten months before admission to the hospital she noticed puffiness of her face, and dryness and roughness of the skin. She also became increasingly sensitive to cold weather. For three months she had noticed that she spoke slowly and that her memory had become distinctly impaired. *Physical examination* showed a puffy and pasty face; gray, coarse, dry hair; dry scaly skin; thickened lips; moderately advanced generalized arteriosclerosis; no cardiac enlargement, a ventricular rate of 70 per minute. She talked very slowly. The blood pressure was 130 mm. Hg systolic and 90 mm. Hg diastolic. The basal metabolic rate was minus 18 per cent on March 13. A total of 11.6 grams of desiccated thyroid gland was given from March 15 to March 26. The basal metabolic rate on the latter date was plus 6 per cent.

M. G. had been treated for myxedema for about five years but six months before our observations she stopped taking thyroid extract. Soon thereafter she developed weakness, puffiness of her face and extreme sensitivity to cold. *Physical examination* showed a well nourished, middle aged woman, with slow deliberate speech; dry, sparse hair; dry, thickened, pasty skin; puffiness under eyes; normal sized heart, with a rate of 60 per minute. The blood pressure was 130 mm. Hg systolic and 80 mm. Hg diastolic. The basal metabolic rate was minus 25 per cent on February 20. Thyroid gland medication was given from February 24 to March 6. During this period she received a total of 12.0 grams of desiccated thyroid gland. The basal metabolic rate on March 6 was minus 3 per cent.

R. F. entered the hospital because of weakness, dizziness and headaches. She had suffered from weakness for one year before admission. About ten months before admission she became very sensitive to cold. Two months before admission she noted increasing dryness of the skin and puffiness of the face. During the week preceding entry to the hospital she had experienced almost constant headache and dizziness. *Physical examination* showed an obese, middle aged woman, with dry coarse hair, puffy face, slow halting speech, dry thick skin, large dry tongue and pads of fat over the clavicles, shoulder blades and hips. The heart was not

enlarged. The ventricular rate was 58 per minute and the blood pressure was 95 mm. Hg systolic and 65 mm. Hg diastolic. The basal metabolic rate was minus 24 per cent. Thyroid gland medication was given from October 4 to October 26. Twelve and eight tenths grams of desiccated thyroid gland were given. The basal metabolic rate on October 27 was plus 14 per cent.

S. M. had suffered from fatigue, lack of ambition, irritability and numbness of fingers and toes for five months. During the four months preceding her entry into the hospital she gained weight steadily without eating more than usual. Her skin had become thick and dry, and she became very sensitive to cold. Two months before admission her hair began to fall out and her irritability of temperament increased, so that she found it hard to get along with people. On *physical examination* she showed a dry, thickened, sallow skin; gray, scanty, dry hair; a heart rate of 60 per minute, and a blood pressure of 120 mm. Hg systolic and 70 mm. Hg diastolic. The basal metabolic rates were minus 24 per cent and minus 21 per cent on February 18 and 21, respectively. Thyroid gland medication was begun on February 21 and ended on March 14. She received a total of 11.3 grams of desiccated thyroid gland. On March 15, the basal metabolic rate was minus 1 per cent.

M. M. had been treated for myxedema for one year. Thyroid gland taken by mouth relieved all symptoms but on cessation of medication five months before entry she gained weight, and became very sensitive to cold. She noted puffiness of the face and tired easily. *Physical examination* showed an obese, middle aged woman with pasty complexion, puffy face, slow mentality and slow speech. Her hair was dry, coarse, and very scanty. The skin was thickened and had a peculiar waxy appearance. The heart was of normal size, with a ventricular rate of 70 per minute. The blood pressure was 115 mm. Hg systolic and 70 mm. Hg diastolic. The basal metabolic rate was minus 33 per cent on March 27. Thyroid gland medication was given from March 28 to April 16. She received a total of 16.4 grams of desiccated thyroid gland during this period. The basal metabolic rate was exactly the average of normal on April 16.

E. Sa. entered the hospital because of excessive gain in weight, constipation, anorexia, and dry hair and skin. She had been feeling well until three months before admission when she began to suffer from obstinate constipation and loss of appetite. She continued to gain weight, however. Then she noted that her hair and skin were getting dry, and that her hair was falling out rapidly. *Physical examination* showed obesity, with fat pads over her clavicles, scapulae and hips; a thickened dry skin, and coarse, sparse, dry hair; a normally sized heart with ventricular rate of 70 per minute and blood pressure of 100 mm. Hg systolic and 70 mm. Hg diastolic. The basal metabolic rate was minus 25 per cent and minus 23 per cent on February 29 and March 2, respectively. Thyroid medication was started on March 6, and omitted on March 26. She received a total of 20.0 grams of desiccated thyroid during this period. The basal metabolic rate on March 26 was minus 2 per cent.

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