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Research Article

STUDIES OF THE CIRCULATION IN PATIENTS SUFFERING FROM SPONTANEOUS MYXEDEMA[1]

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It has been demonstrated that changes occur in the heart in the presence of myxedema. In 1918, Zondek (1) first described the large sluggish heart, bradycardia, and certain alterations in the electrocardiogram. Since then Assmann (2) has shown that the use of thyroid extract results in the reduction in the size of the heart, but that digitalis is without effect in this respect. Hallock (3) reported fall in blood pressure, decrease in the size of the heart, weight loss, increase in vital capacity, and alterations in the electrocardiogram following the administration of thyroid extract. Means (4) studied the relationship between the basal metabolic rate, the pulse, and the cardiac output. Venous pressure is not significantly affected by the use of thyroid extract (5). Altschule and Volk (6) studied the volume output, the work of the heart, and the circulation rate in hypothyroidism induced by total ablation of the thyroid gland. They found the minute volume decreased in seven patients, the arteriovenous oxygen difference of the blood increased, and the blood velocity in most instances slower than normal.

We have had occasion to make studies of four patients suffering from spontaneous myxedema. Although previous workers have studied individual functions of the heart and circulation in this disease, observations have not been recorded in which the several functions have been correlated in the same patient both before and during treatment with thyroid extract.[2]

METHODS

All patients were free of the signs of congestive heart failure. Observations were made in the morning while the patients were in a basal metabolic state. Measurements of the cardiac output were made by the acetylene method, three samples of gas being taken as recommended by Grollman (7), and further elaborated by Grollman, Friedman, Clark, and Harrison (8). During this measurement the patients were sitting in a steamer chair (angle 135 degrees) with legs extended. They were trained to carry out the procedures beforehand. While resting quietly the radial pulse was counted at intervals of five minutes. At the end of one-half hour the acetylene air mixture was rebreathed. Three samples of the gas were then taken during each rebreathing period for estimation of the arteriovenous oxygen difference. Three periods of rebreathing were carried out on each patient. Shortly afterward, the oxygen consumption was measured with a Benedict-Roth spirometer. After a short pause, the vital capacity was measured and the height and weight recorded. Then the patient rested again, lying down. In succession, sufficient time being allowed between each procedure for the patient to return to a basal state, an electrocardiogram was taken, the arm to tongue circulation time recorded, the venous pressure estimated, and the blood pressure measured. Finally, an x-ray photograph of the heart was made at a distance of two meters.

The arm to tongue circulation time was estimated by the use of decholin: 5 cc. of a 20 per cent solution were injected rapidly (1 to 2 seconds) through an 18 gauge needle into an antecubital vein while the patient was lying quietly in the prone position. This was repeated in one and one-half minutes after the response to the first test had been elicited. The time was recorded from the beginning of the injections until the patient perceived the bitter taste. The injection time was also recorded; since, however, the response may come with a minimum amount of the drug, the time which we have used was taken from the start, rather than from the conclusion of the injection. The same vein, either right or left, was used in each patient for the injections.

The venous pressure was measured by the direct method (9) using a large antecubital vein, the vein being placed on a level with the right auricle. The apparatus consisted of an L-shaped tube of glass attached to a three-way stopcock, syringe, and an 18 gauge needle. The apparatus was filled with a solution of sterile, normal saline, a venipuncture performed, and the direct pressure readings recorded. Normal pressures with this apparatus range from 4.0 to 9.0 cm. of saline. The same vein was used for subsequent observations and the other one for the estimation of the circulation time.

X-ray photographs of the heart were taken with the

[1] Read by title before the Twenty-Eighth Annual Meeting of the American Society for Clinical Investigation Held in Atlantic City, New Jersey, May 4, 1936.

[2] We wish to express our indebtedness to the Metabolism Division of the Department of Medicine for its cooperation and permission to study these patients.

TABLE I

Data of five patients suffering from myxedema

Case, hospital number, age, and sex	Date	Body surface	Oxygen consumption	Basal metabolic rate	Arteriovenous oxygen difference	Cardiac output	Cardiac output	Heart rate	Cardiac output	Cardiac area	Cardiac volume	Arterial pressure	Left ventricular work	Circulation time	Venous pressure	Vital capacity	Red blood count	Hemoglobin
		sq. m.	*cc. per minute*	*per cent*	*cc.*	*liters per minute*	*liters per sq. m. per minute*	*per minute*	*cc. per beat*	*sq. cm.*	*cc.*	*mm. Hg*	*gram meters per beat*	*seconds*	*cm. saline*	*cc.*	*millions*	*per cent*
Case 1, M. R.	Feb. 6, 1935	1.89	147	−33	75.6	1.95	1.03	74	26.3	149.6	1667	120/80	36.0	19.8	7.0	1900	4.7	100
Number 84434	Feb. 12, 1935	1.89	137	−37	70.3	1.95	1.03	68	28.7	147.2	1628	118/80	39.0	21.3	5.3	2100		
62 years ♀	Feb. 24, 1935. Thyroid extract started																	
	Mar. 28, 1935	1.82	187	−12	62.9	2.97	1.63	76	39.0	138.7	1490	124/76	53.0	15.0	8.5	2050		
	April 17, 1935	1.80	207	− 1	56.2	3.68	2.04	76	48.0	133.3	1403	120/52	56.0	14.4	5.0	2100		
	May 10, 1935	1.78	203	− 3	59.5	3.41	1.92	80	42.6	123.1	1261	140/64	59.0	13.8	7.3	2100		
	June 2, 1935. Thyroid extract discontinued																	
	June 20, 1935	1.79	162	−22	70.2	2.31	1.29	70	33.0	121.1	1217	108/58	37.0	16.9	5.4	2300		
Case 2, K. B.	Mar. 1, 1935	1.68	162	−20	73.5	2.20	1.31	64	34.0	144.9	1606	134/90	52.0	19.6	7.3	2800	4.1	100
Number 86248	Mar. 7, 1935. Thyroid extract started																	
50 years ♀	April 6, 1935	1.67	189	− 5	65.5	2.89	1.73	70	41.0	146.3	1612	160/90	70.0	18.3	9.5	2700		
	June 21, 1935	1.62	207	+ 7	58.9	3.51	2.16	64	55.0	131.7	1378	122/76	74.0	11.5	8.8	2500	4.4	85
Case 3, M. M.	May 23, 1935	1.68	120	−39	82.0	1.46	0.87	66	22.0	113.7	1105	130/80	31.0	22.6	6.8	1900	3.8	73
Number 97914	June 1, 1935. Thyroid extract started																	
59 years ♀	June 27, 1935	1.65	153	−21	68.0	2.25	1.36	75	30.0	104.5	973	122/70	39.0	19.0	6.8	2300		
	July 12, 1935	1.63	170	−12	60.3	2.82	1.73	90	31.4	102.0	940	112/68	38.0	17.6	5.9	2250		
Case 4, A. H.	Feb. 3, 1936	1.94	166	−32	67.8	2.45	1.26	68	36.0	154.9	1757	105/78	45.0	14.6	9.9	3250	3.7	67
Number 119047	Feb. 9, 1936. Thyroid extract started																	
26 years ♀	Mar. 4, 1936	1.90	180	−25	66.7	2.70	1.42	84	32.0	149.4	1670	112/80	42.0	12.6	8.7	3200	4.3	74
	Mar. 18, 1936	1.86	209	−10	65.4	3.20	1.72	82	40.0	117.9	1167	116/74	52.0	11.2	7.6	3200	4.3	74
	April 8, 1936	1.81	226	0	61.0	3.71	2.05	92	43.0	115.6	1132	128/80	61.0	9.9	7.7	3100	4.4	74
Case 5, M. S.	April 18, 1934. Thyroid extract started																	
Number 61241	April 24, 1934	1.64	172	−20	73.5	2.34	1.43	80	29.0	137.3	1466	156/106	52.0			2980	4.9	100
47 years ♂	Oct. 10, 1935. On thyroid extract																	
	Oct. 10, 1935	1.63	178	−16	74.0	2.41	1.48	68	35.0	134.8	1448	158/98	59.0	20.2	5.8	3200		

patients in the standing position, in full inspiration, at a distance of two meters. Measurements of the heart were carried out by the technique of Levy (10), and estimations of volume were made as recommended by Bardeen (11). The volumes recorded in Table I have not been multiplied by the constant which is in Bardeen's formula. This was done in order to make our observations comparable to those of Starr, Collins, and Wood (12).

OBSERVATIONS

Case 1. M. R., Hospital Number 84434, a 62-year-old woman, had gained 45 pounds following menopause 12 years previously. For the past 10 years she had noticed increased sensitivity to cold; and for 8 years she had experienced dyspnea on exertion and puffiness of the eyes. Six years ago she was in a hospital 3 weeks because of weakness and dyspnea, and was given thyroid extract for 6 months. Mental dullness had been observed for 3 or 4 years.

She was admitted to the hospital February 2, 1935. She was obese and exhibited myxedematous facies, slow speech, and slow reaction time. The hair was coarse, dry, and scant. The lips were slightly cyanotic. The lungs were clear; the heart sounds were distant but clear. The aortic second sound was louder than the pulmonic. The liver was 7 cm. below the costal margin in the midclavicular line. There was no edema. The count of the red blood cells was 4.72 millions and the hemoglobin 100 per cent (Sahli) (14.5 grams of hemoglobin equivalent to 100 per cent). On February 6, 1935, the basal metabolic rate was —33 per cent (Table I, Figure 1). The cardiac output per minute was 1.95 liters or 1.03 liters per square meter of body surface amounting to 26.3 cc. per beat. The arteriovenous oxygen difference was 75.6 cc. The cardiac area measured 149.6 sq. cm., and the circulation time 19.8 seconds, and the venous pressure 7.0 cm. of saline. The systolic blood pressure measured 120 mm. Hg and the diastolic 80 mm. Hg. The heart rate was 74 per minute. The vital capacity measured 1900 cc. These measurements were repeated on February 12, 1935, and were essentially the same, except that the basal metabolic rate was —37 per cent, the circulation time 21.3 seconds, and the vital capacity 2100 cc.

Desiccated thyroid extract (Armour) was first administered February 24, 1935, the patient receiving 0.015 gram a day; this was increased to 0.03 gram on March 3, to 0.06 gram on March 7, to 0.10 gram on March 15, to 0.12 gram on March 21, and to 0.18 gram on March 23.

On March 29, 1935, the basal metabolic rate had risen to —12 per cent and the weight had decreased. At this time the cardiac output per minute had increased to 2.97 liters, or 1.63 liters per square meter of body surface, amounting to 39 cc. per beat. The arteriovenous oxygen difference decreased to 62.9 cc., and the cardiac area to 138.7 sq. cm. The circulation time decreased to 15.0 seconds. The vital capacity and the arterial and venous pressure remained essentially the same.

With continuation of thyroid extract the basal metabolic rate rose to —1 per cent on April 17, 1935, and the

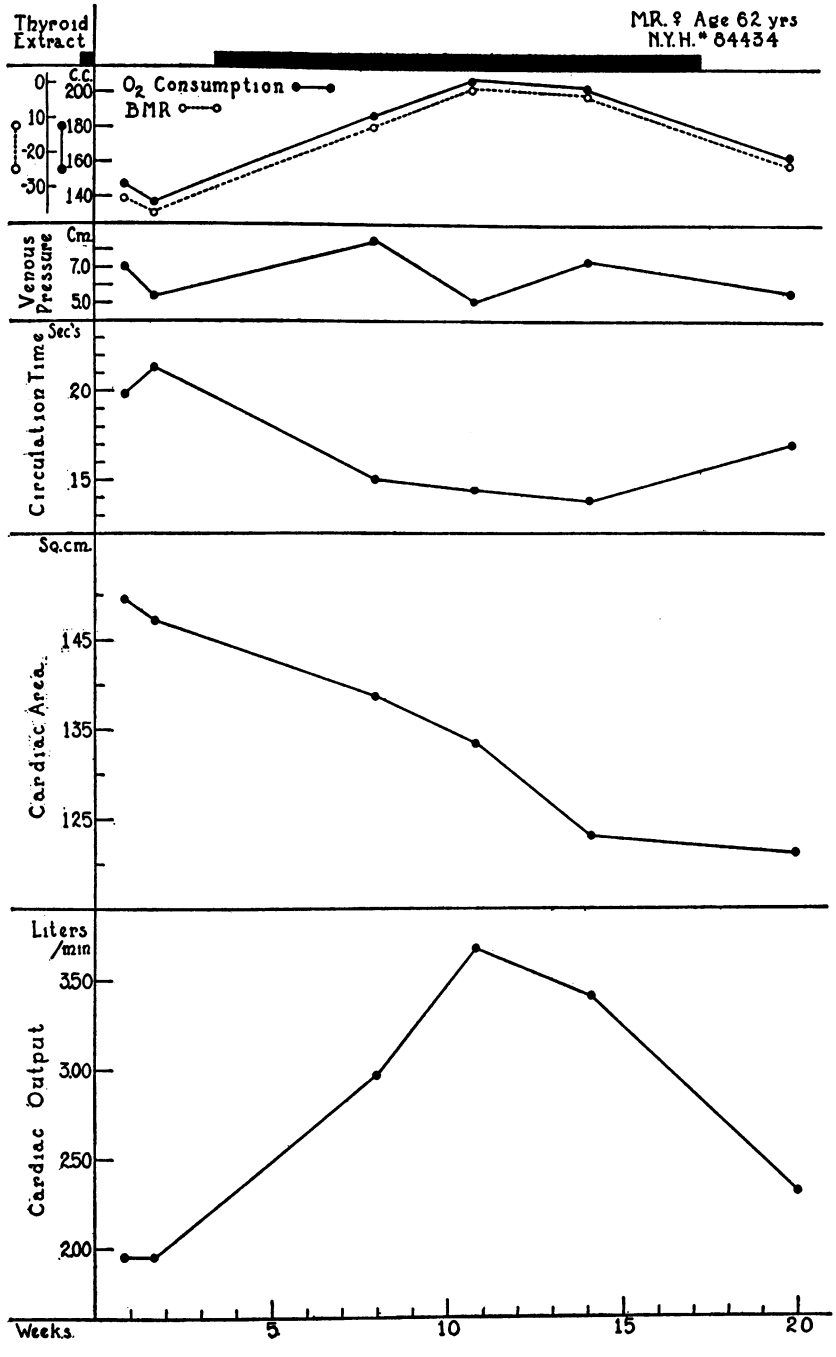

FIG. 1. THE EFFECT OF THYROID EXTRACT ON THE OXYGEN CONSUMPTION, THE BASAL METABOLIC RATE, THE VENOUS PRESSURE, THE CIRCULATION TIME, THE CARDIAC AREA, AND THE CARDIAC OUTPUT OVER A PERIOD OF 20 WEEKS IN M. R., CASE 1.

The last measurements were made 18 days after thyroid extract had been discontinued.

weight decreased further. The cardiac output per minute increased to 3.68 liters, the output per beat to 48 cc., and the output per square meter of body surface to 2.04 liters per minute. The arteriovenous oxygen difference had decreased further to 56.2 cc., and the cardiac area to 133.3 sq. cm. The circulation time decreased to 14.4 seconds. The systolic blood pressure measured 120 mm. Hg and the diastolic 52 mm. Hg.

When the measurements were repeated on May 10, 1935, there was no essential change except that the heart had decreased in size further to 123.1 sq. cm. At this time it may be stated that the measurements were within normal limits.

Thyroid extract was discontinued on June 2, 1935, and as a consequence on June 20, the basal metabolic rate had fallen to —22 per cent and the weight had increased slightly. The cardiac output per minute decreased to 2.31 liters amounting to 33 cc. per beat and 1.29 liters per square meter of body surface. The cardiac area remained unchanged (121.1 sq. cm.). The arteriovenous oxygen difference had widened to the pre-therapy level (70.2 cc.) and the circulation time had lengthened to 16.9 seconds. The systolic blood pressure recorded 108 mm. Hg; the diastolic 58 mm. Hg.

In this patient we had the opportunity of observing the improvement of the circulation with thyroid therapy as well as the effect of its discontinuance.

Case 2. K. B., Hospital Number 86248, was a 50-year-old white housewife who, over a period of 5 years, had shown weakness, cyanosis, coldness of the hands, hoarseness of the voice, increase in body weight, puffiness of the hands, face, and legs, and mental apathy. She had taken thyroid tablets from February 1 to February 5, 1935 (total, 0.6 gram).

She was admitted to the hospital February 28, 1935. At that time her face was puffy, florid, and cyanotic. The skin was dry and thick. The voice was husky and there were supraclavicular pads of fat. The lungs were clear, and there was no pitting edema. The heart rhythm was regular; no murmurs were heard. The aortic second sound was louder than the pulmonic. The liver was not palpable. The systolic blood pressure measured 160 mm. Hg; the diastolic 110 mm. Hg. The count of the red blood cells was 4.3 millions and the estimation of the hemoglobin 100 per cent.

The basal metabolic rate was —20 per cent on March 1, 1935. At this time the cardiac output per minute was 2.2 liters, amounting to 1.31 liters per square meter of body surface and 34 cc. per beat. The arteriovenous oxygen difference measured 73.5 cc., and the cardiac area 144.9 sq. cm. The circulation time was 19.6 seconds, and the venous pressure was 7.3 cm. of saline. The systolic blood pressure measured 134 mm. Hg and the diastolic 90 mm. Hg and the vital capacity 2800 cc. The heart rate was 64 per minute.

Beginning March 7, 1935, thyroid extract, 0.03 gram, was given daily. This was slowly increased to 0.12 gram a day by May 21, and was associated with definite improvement in her mental activity and decrease in puffiness and coldness of her extremities.

Studies were carried out on April 6 and June 21, 1935, when the basal metabolic rate had risen to —5 per cent and +7 per cent respectively (Table I). The cardiac output per minute, per beat, and per square meter of body surface showed a progressive increase. The weight decreased, the arteriovenous oxygen difference fell to normal, and the cardiac area decreased. The circulation time became shorter and the pulse pressure widened. The heart rate and venous pressure remained essentially unchanged. The clinical improvement was also marked. She was discharged June 1, 1935.

Case 3. M. M., Hospital Number 97194, a 59-year-old married Swiss housewife, had been well until 4 years before admission. She had been somewhat sensitive to cold for approximately 10 years, requiring more clothing than usual. Four years previous to admission she observed a feeling of "gas in the abdomen" and "spells of shaking and jumping sensations in the legs." For 2 years she had been aware of dryness of the skin and dryness and coarseness of the hair which began to fall out rapidly. Puffiness of the eyes, slowness of speech, increasing fatigue, dyspnea, and swelling of the feet had been present for one year.

She was admitted to the hospital May 13, 1935. She was a slightly dyspneic, obese woman. The hair was dry and coarse, the eyebrows scanty, the eyelids puffy, the facies myxedematous, the speech slow, and the skin dry and scaly. A few moist râles were present at both lung bases. The heart sounds were distant, and there were no murmurs. The liver and spleen were not enlarged, and there was no edema. On May 14, the count of the red blood cells was 3.85 millions, and the estimation of the hemoglobin 73 per cent.

On May 23, 1935, when the basal metabolic rate was —39 per cent (Table I) the cardiac output per minute measured 1.46 liters, equivalent to 0.87 liter per square meter of body surface, and the output per beat 22 cc. The arteriovenous oxygen difference was 82.0 cc. The cardiac area measured 113.7 sq. cm. The circulation time recorded 22.6 seconds, and the venous pressure 6.8 cm. The systolic blood pressure measured 130 mm. Hg; the diastolic 80 mm. Hg, and the vital capacity 1900 cc.

On June 1, 1935, desiccated thyroid, 0.015 gram, was given; on June 18 it was increased to 0.03 gram, and to 0.06 gram on June 21. The basal metabolic rate had risen to —21 per cent on June 27. The weight had remained the same, but the cardiac output per minute and per beat had increased as had the heart rate, and vital capacity. The arteriovenous oxygen difference, the circulation time, and cardiac area had decreased. The venous pressure remained unchanged.

Thyroid extract was increased to 0.12 gram per day on July 2, and on July 12 the measurements were again recorded. At this time all measurements were almost within normal limits. The patient showed marked clinical improvement and was discharged on July 14, 1935.

Case 4. A. H., Hospital Number 119047, a 26-year-old married woman was first seen in the New York Hospital December 31, 1935, complaining of swelling of the face and hands of 4 to 6 years' duration. She was admitted

to the hospital on January 23, 1936. A normal pregnancy had occurred 6 years previously, followed by cessation of menstruation for one year. She gave birth after this to one child each year for the following 3 years, making a total of 4 pregnancies. The menses had been regular for the year preceding admission.

Four months after the birth of her first child she noticed puffiness of the eyelids, face and lips. These symptoms disappeared in a few weeks when she was given "injections." These symptoms reappeared with her second pregnancy 4 years before admission and had been present in varying degrees since then. She observed that the skin of the hands and arms became dry and rough. There was loss of interest in reading and definite impairment of memory. There was dyspnea on moderate exertion for the past year.

The face, which was puffy, revealed a stolid expression. The skin was coarse, and the eyebrows were scant. The lungs were clear; the cardiac rate was slow; there were no murmurs; the liver was not enlarged, and edema was not present. The hemoglobin measured 67 per cent and the count of the red blood cells was 3.9 millions. The blood cholesterol amounted to 430 mgm. per cent. On January 25, 1936, the basal metabolic rate was —35 per cent. The electrocardiogram revealed incomplete heart block in which the P–R conduction time was 0.52 second.

Studies made on February 3, 1936, when the basal metabolic rate was —32 per cent (Table I), showed the cardiac output per minute to be 2.45 liters or 1.26 liters per square meter of body surface, amounting to 36 cc. per beat. The arteriovenous oxygen difference was 67.8 cc., and the cardiac area measured 154.9 sq. cm. The circulation time measured 14.6 seconds and the venous pressure 9.9 cm. of saline. In short, this patient exhibited a practically normal arteriovenous oxygen difference and circulation time.

The use of thyroid extract, 0.008 gram per day, was instituted February 9, 1936. This dosage was gradually increased to 0.01 gram a day by March 4, when the basal metabolic rate had increased to —25 per cent, the hemoglobin estimation to 74 per cent, and the count of the red blood cells to 4.3 millions. Observations were repeated March 4 as well as on March 18 and April 8, when the basal metabolic rate was —10 per cent and 0 respectively. At this time the dose of thyroid extract was 0.18 gram a day. The weight decreased and the cardiac output per minute increased to 3.71 liters per minute or to 2.05 liters per square meter of body surface and amounted to 43 cc. per beat. The arteriovenous oxygen difference decreased slightly to 61.0 cc., the cardiac area to 115.6 sq. cm., and the circulation time to 9.9 seconds. The blood pressure rose, and the pulse rate increased to 92 per minute. The P–R conduction time decreased to 0.30 second.

She was discharged April 10, 1936, more alert and active. The P–R conduction time remained prolonged. The arteriovenous oxygen difference in this patient, when she was myxedematous, was not increased as in the other patients. The bearing of anemia on this will be discussed later (see p. 243).

Case 5. M. S., Hospital Number 61241, a 47-year-old Jewish electrician was admitted to the hospital on April 1, 1934. In 1929 he experienced for the first time attacks of epigastric pain which gradually increased in severity. On November 15, 1933, he was admitted to the Beth Israel Hospital (Boston). The diagnosis of angina pectoris was made, and total ablation of the thyroid gland was performed. The basal metabolic rate was —20 per cent on the 25th postoperative day, and he showed definite improvement on performing an exercise tolerance test. On discharge he was taking thyroid extract 0.015 gram a day. On the 90th postoperative day the basal metabolic rate was —17 per cent, and he was complaining again of pain on exertion. On the 160th postoperative day the basal metabolic rate had decreased to —27 per cent. He was then given daily 100 mgm. of dinitrophenol and 0.015 gram of thyroid extract. Although he took dinitrophenol irregularly, he developed blurring of the vision and vague paraesthesias of the legs. He was admitted to the New York Hospital April 1, 1934. At this time the pulse was 80 per minute, the respiration 20 per minute; the blood pressure measured 150 mm. Hg systolic and 100 mm. Hg diastolic.

He was a short, stocky, middle aged man whose skin was slightly dry, thickened, and rough. He was mentally alert, but his speech was slightly thick. There was no cyanosis, dyspnea, nor edema. The heart was at the upper limits of normal in size, the rhythm regular, the rate slow. There was a blowing systolic murmur at the apex, replacing the first sound. The lungs were clear. The liver was palpable 2 cm. below the right costal margin in the midclavicular line. The count of the red blood cells was 4.91 millions and the hemoglobin amounted to 100 per cent. The urine showed a trace of albumin; in the phenolsulphonpthalein test he excreted 51 per cent in 2 hours. The basal metabolic rate ranged between —17 and —25 per cent. The use of thyroid extract (0.015 gram) was begun April 18, 1934, from which he experienced symptomatic improvement.

Circulatory studies were performed April 24, 1934, at a time when the basal metabolic rate was —20 per cent. The cardiac output per minute measured 2.34 liters, equivalent to 1.43 liters per square meter of body surface, amounting to 29 cc. per beat. The arteriovenous oxygen difference amounted to 73.5 cc. and the cardiac area to 137.3 sq. cm.

Measurements were repeated on October 10, 1935, when the basal metabolic rate was —16 per cent. At this time he was taking approximately 0.006 gram of thyroid a day. In general all the measurements were essentially the same as they had been 18 months before. The circulation time was prolonged to 20.2 seconds.

In all the patients studied, when the basal metabolic rate was low during the myxedematous state, the cardiac output per minute and per beat were diminished, the arteriovenous oxygen differ-

ence increased (exception A. H., Case 4), and the circulation time prolonged. Treatment with thyroid extract resulted in a rise in the basal metabolic rate and was associated with changes in these functions to or toward normal levels. As these changes progressed, the heart became smaller in each instance. Moreover, there can be demonstrated quantitative relationships between these changes, not only for an individual patient, but also for all patients when the data are pooled. For example, in these patients, as the oxygen consumption increased with the administration of thyroid extract the circulation time became shorter, a linear relationship being maintained (Figure 2). There is also a correlation between the oxygen consumption and the arteriovenous oxygen difference, which assumes a linear relationship (Figure 3). In short, as the arteriovenous oxygen differences become smaller and approach normal (60.0 cc.) the oxygen consumption

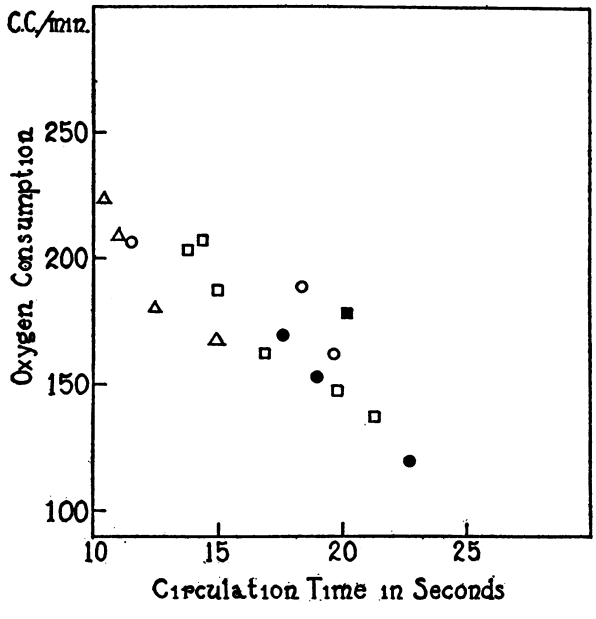

FIG. 2. RELATIONSHIP BETWEEN THE OXYGEN CONSUMPTION AND THE CIRCULATION TIME AS IMPROVEMENT OCCURRED ON THYROID THERAPY.

In this figure as well as in Figures 3, 4, and 5, each of the five patients studied is represented by a different symbol. An open square represents Case 1, M. R.; an open circle represents Case 2, K. B.; a solid dot represents Case 3, M. M.; a triangle represents Case 4, A. H.; and a solid square represents Case 5, M. S. The circulation time becomes shorter as the oxygen consumption increases.

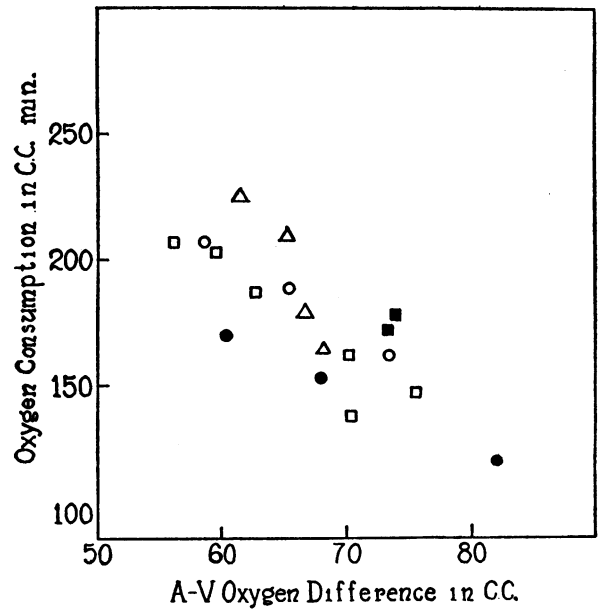

FIG. 3. CORRELATION BETWEEN THE OXYGEN CONSUMPTION AND THE ARTERIOVENOUS OXYGEN DIFFERENCE

As the oxygen consumption of each individual increases on thyroid therapy the arteriovenous oxygen difference becomes less.

increases. In a similar fashion, there is a linear correlation between the basal metabolic rate and the arteriovenous oxygen difference (Figure 4), since the arteriovenous oxygen difference becomes less with the rise in the basal metabolism until normal relationships are established at 60.0 cc. arteriovenous oxygen difference, and zero basal metabolic rate. Finally, a linear relationship is found in these patients between the circulation time and the cardiac output per minute; as the cardiac output increases, the circulation time becomes shorter (Figure 5).

The venous pressure in these patients was not elevated during the myxedematous state and showed no uniform changes as the basal metabolic rate rose to normal.

The size of the heart decreased markedly on thyroid therapy in all patients except in Case 5; no attempt was made to raise the metabolic rate of this patient to normal by use of thyroid extract. The greatest diminution in size occurred in Case 4 amounting to 25 per cent of the initial size measured before thyroid extract was administered. The smallest reduction occurred in Case 2 amounting to 9.7 per cent of the initial

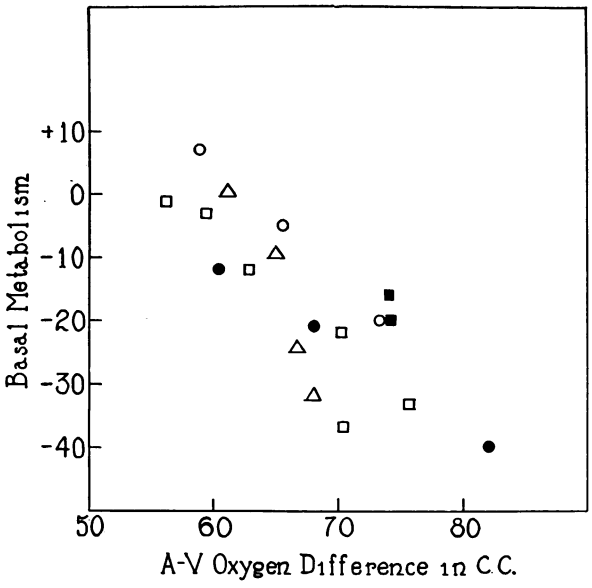

FIG. 4. CORRELATION BETWEEN BASAL METABOLIC RATE AND THE ARTERIOVENOUS OXYGEN DIFFERENCE

As the basal metabolic rate increases the arteriovenous oxygen difference decreases.

size. The case of M. R. (Case 1) serves to illustrate these changes (Figure 6).

DISCUSSION

The myxedematous state in these patients was associated with a low basal metabolic rate, with decrease in cardiac output per minute and per beat, with increase in the arteriovenous oxygen difference, and slowing of the velocity of the blood flow. This was a reversible state since the administration of thyroid extract was associated with alterations toward the normal levels of these functions and with shrinking in the cardiac size.

The finding of a widened arteriovenous oxygen difference during the myxedematous state is somewhat puzzling. In the myxedematous state, it appears that, even though the circulatory needs of the body are markedly lowered, the heart does not maintain a circulation adequate for these lowered requirements, since the arteriovenous oxygen difference increases. In short, the velocity of the blood flow may be so slow that greater amounts of oxygen are removed from each unit of blood than normally occurs. Boothby and Rynearson (13) proposed the hypothesis that in the hyperthyroid state there is present in the organism a special circulatory stimulant, which causes a greater increase in the circulation rate than occurs in a normal subject as the result of a corresponding increase in oxygen consumption due to work. In the myxedematous state it may be possible that the opposite is the case, namely that the circulation becomes abnormally slow in comparison to the oxygen consumption because of the lack of such a substance. Thyroid therapy in this state, however, apparently supplies a substance which in addition to increasing the oxygen consumption of the body also stimulates the circulatory apparatus to return to such an efficient state that the arteriovenous oxygen difference becomes normal. Our observations lend weight to Boothby and Rynearson's hypothesis. The slowing of the velocity of the blood flow and the decrease in cardiac output in the myxedematous state are apparently brought about by factors different from those present in congestive failure (14).

In Case 4, A. H., there occurs an additional factor which leads to interesting observations. This patient, as has been stated before, was anemic. Although the basal metabolic rate was low (— 39 per cent) in the presence of a rather severe myxedematous state, the arteriovenous

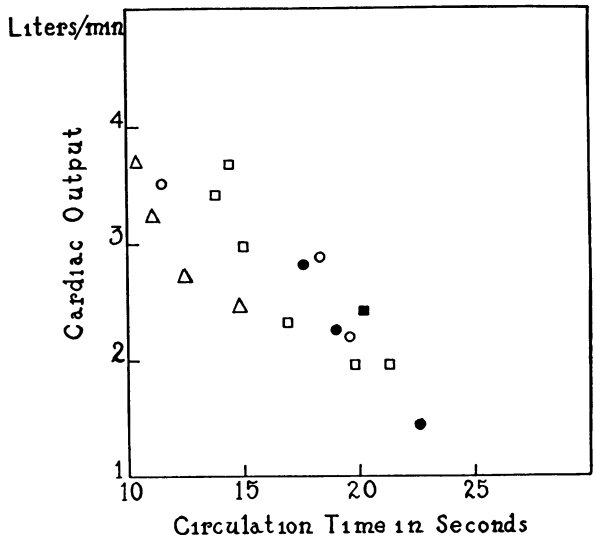

FIG. 5. LINEAR RELATIONSHIP BETWEEN THE CARDIAC OUTPUT AND THE CIRCULATION TIME AS IMPROVEMENT OCCURRED WITH THE USE OF THYROID EXTRACT

As the cardiac output increases the circulation time becomes shorter.

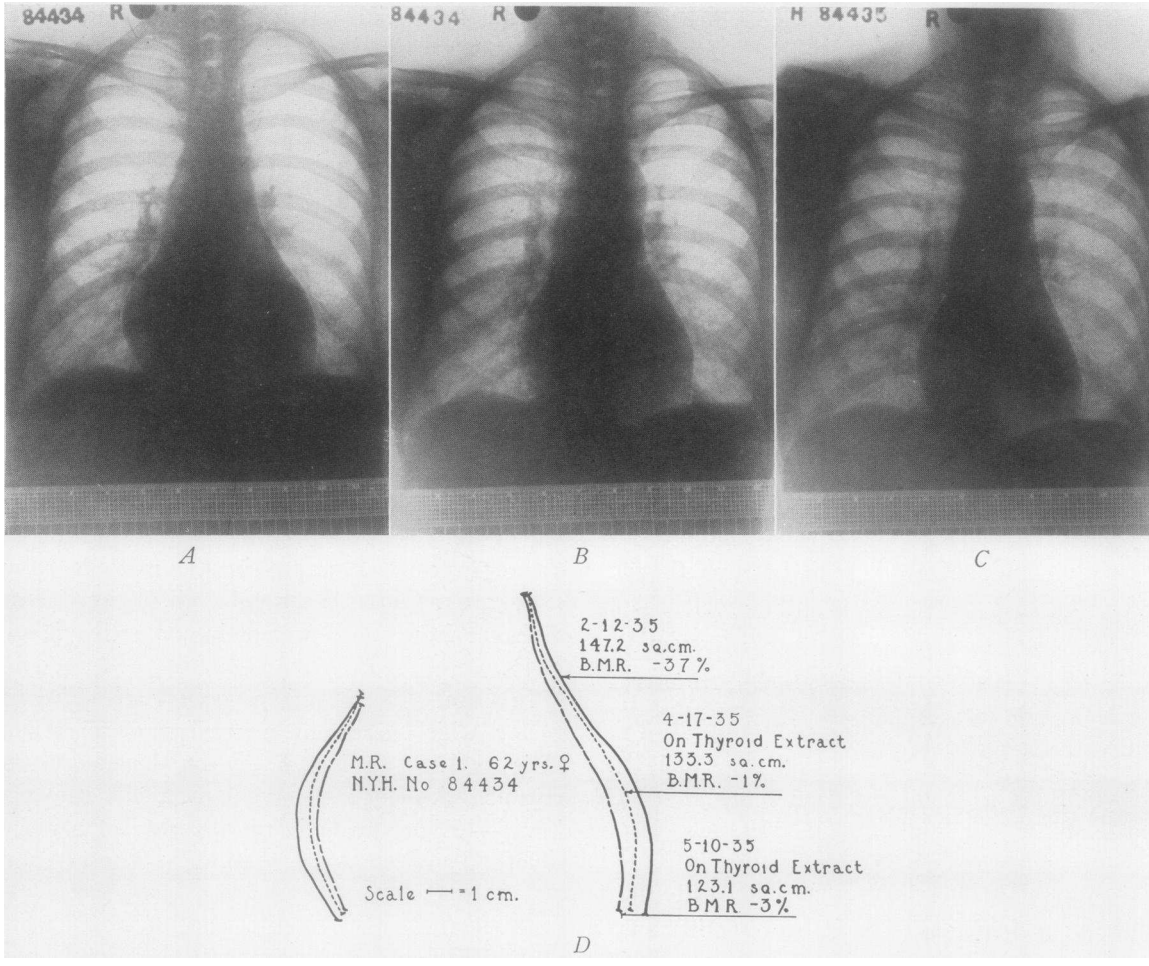

FIG. 6. PHOTOGRAPHS OF X-RAYS OF M. R., CASE 1

Photograph *A* was taken on February 12, 1935, at a time when the basal metabolic rate was — 37 per cent, before thyroid extract was given. Photograph *B* was taken on March 7, 1935, after the basal metabolic rate had risen to — 17 per cent, on the administration of thyroid extract. Photograph *C* recorded the size of the heart on May 10, 1935, when the basal metabolic rate was 0 per cent. *D* represents outlines of the heart traced from the x-ray protographs *A*, *B*, and *C* on thin paper and superimposed in the manner shown.

oxygen difference was at the upper limits of normal, and moreover the velocity of blood flow was well within normal limits. It is recalled that in the other patients the arteriovenous oxygen difference was increased as well as the circulation time. It has been shown by Stewart, Crane and Deitrick (15) and others (16, 17) that anemia speeds up the circulation rate. On the basis of this evidence it appears that this factor was accountable for the normal arteriovenous oxygen difference in this patient in whom we would have otherwise expected an increase. If this is the situation, it indicates that the circulatory apparatus in myxedema is able to respond in a normal fashion to factors other than thyroid extract. The data on this patient lend evidence to our belief that the wide arteriovenous oxygen difference in myxedema is owing to the slow velocity of blood flow.

Another question which might be raised is whether the entire circulatory system is affected by thyroid therapy or whether the heart is especially susceptible. It appears from our correlations that the decrease in the circulation time and the decrease in the arteriovenous oxygen difference following therapy correspond very

closely to the decrease in heart size and to its increased output and work per beat (see p. 247).

We had the opportunity of studying one of the patients, M.R., Case 1, after thyroid extract had been discontinued, and to make deductions relating to the duration of its effect. June 20, 18 days after thyroid extract had been discontinued (Figure 1), the heart remained small, although the basal metabolic rate was now—22 per cent; nevertheless it was less efficient than when it had been larger in size with the basal metabolic rate —1 per cent or —3 per cent. This indicates that heart size alone, in this state, is not the only factor regulating its efficiency. It is apparent, by inference, that thyroid extract might have affected the muscle directly when it was given or that in its absence the circulation had lacked the stimulating factor. In spite of this decrease in efficiency, the circulation was nevertheless still considerably more adequate than it was before thyroid therapy was first instituted. It appears that the effect of thyroid therapy persists, at least longer than 18 days (Figure 7) since the work of the heart in proportion to its size did not drop along the same line as it had risen on thyroid therapy. These differences are perplexing and we believe warrant further study. In short, certain effects of the lack of thyroid hormone probably appear only after a long period of deprivation while the changes in basal metabolic rate take place in a shorter time.

Electrocardiograms of these patients were taken at frequent intervals both before and after the institution of therapy. In the patients suffering from spontaneous myxedema, before therapy was begun, the QRS complexes were of low amplitude and slightly split. The T-waves in all three leads were of low amplitude. T_1 was negative in one (Case 1) and diphasic in another patient (Case 2) and "coved" in both. T_3 was diphasic in three patients (Case 1, Case 2 and Case 3). There was right axis deviation in two (Case 3 and Case 4) and left axis deviation in two (Case 1 and Case 2). The P–R conduction time was prolonged in one (Case 4) and at the upper limits of normal in two others (Case 2 and Case 3). The chest lead [3] was characterized by very small Q-waves, moderately low R-waves, and low voltage T-waves which were negative, but with a slight positive phase in two instances (Case 1 and Case 3).

[3] The chest lead was derived from the right arm electrode placed just within the apex and the left arm electrode placed in the interscapular region (18).

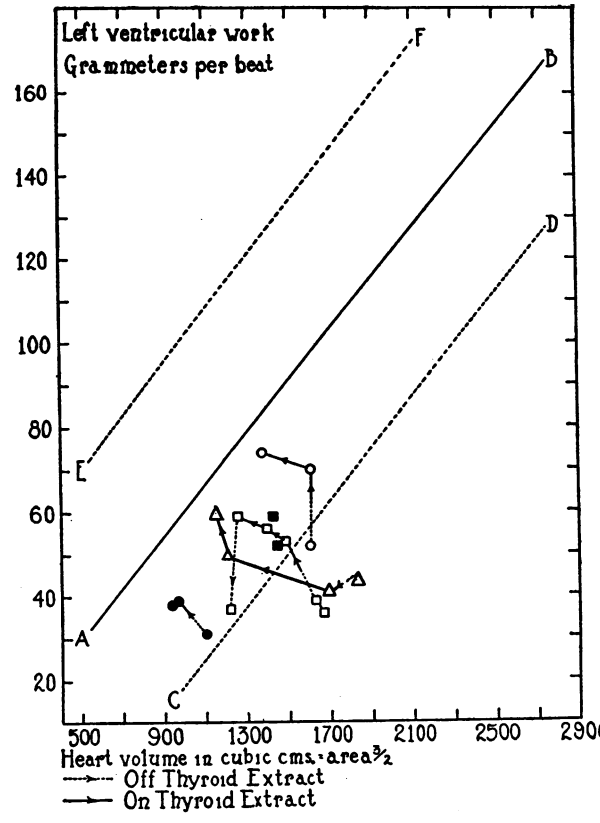

FIG. 7. LEFT VENTRICULAR WORK PER BEAT AND CARDIAC VOLUME

The data from Table I relating to work of the left ventricle per beat are plotted against the corresponding cardiac volumes. Line *AB* represents the best line, the regression of the work on the area, defined by Starr, Collins and Wood (12, Figure 2) on the basis of a statistical treatment of data from a control group of cases. Lines *CD* and *EF* are placed by these authors at a distance of twice the standard deviation from *AB*. It appears from their observations that a patient falling within the zone *CD–EF* has a normal circulatory function, that is to say, the work of the heart is commensurate with its size; on the other hand, they found that the values relating to patients who had suffered from cardiac decompensation, fell in a zone below *CD*. In the myxedematous state before thyroid extract was administered, three of the patients studied fell outside the line *CD* while the other two fell just within the line *CD*. After therapy all the patients moved up into the normal zone, toward the line *AB*.

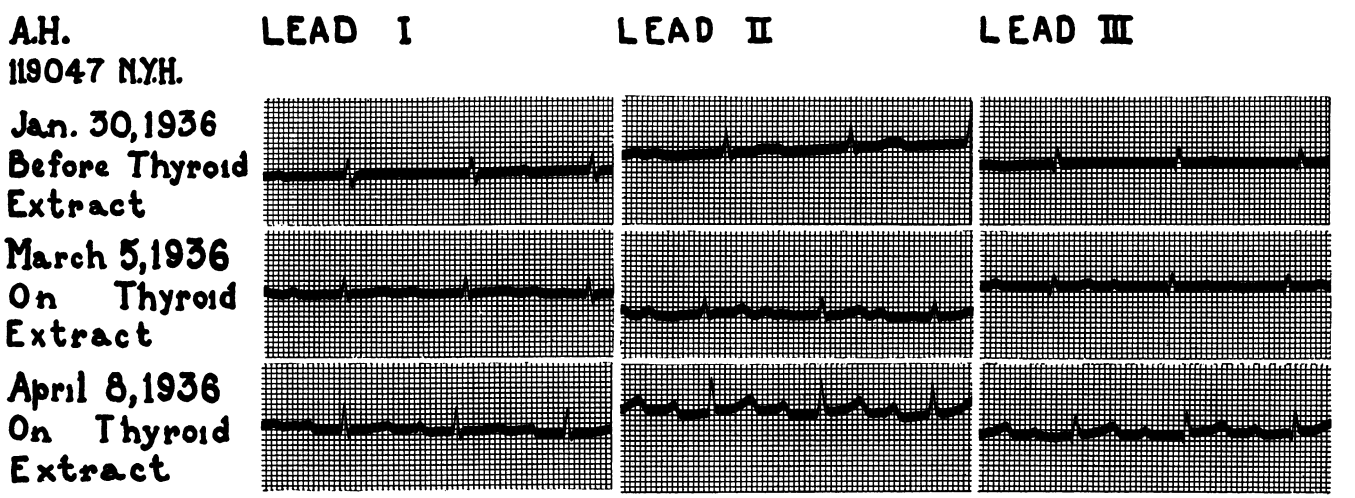

FIG. 8. CHANGES OCCURRING IN THE ELECTROCARDIOGRAM OF A. H., CASE 4, WHEN GIVEN THYROID EXTRACT

The first record was taken on January 30, 1936, before thyroid extract had been administered when the basal metabolic rate was —36 per cent. The second record was taken on March 5, 1936, after the extract had been given for 24 days and the basal metabolic rate had increased to —24 per cent. The third record was taken on April 8, 1936, 33 days later still when the basal metabolic rate had risen to 0 per cent. Divisions of the ordinates equal 10^{-4} volts. Divisions of the abscissae equal 0.04 of a second. The standardization is such that 1 cm. deflection of the string is equivalent to 1 millivolt. The original curves are sharply contrasted black and white; no half tones are lost by this method of reproduction. The electrocardiograms are reduced to two-thirds their natural size.

Following the administration of thyroid extract, the QRS complexes and the T-waves increased in amplitude. The two patients exhibiting right axis deviation beforehand, now showed left axis deviation. The P–R conduction time decreased in all four cases, even though it was not prolonged during the myxedematous state. In the chest lead the Q-waves increased in amplitude and the T-waves became more negative in two cases (Case 1 and Case 3). The electrocardiographic records of A. H. (Case 4) serve to illustrate certain of these changes (Figure 8).

In the case of M. R. (Case 1) there was occasion to observe the electrocardiograms first before thyroid extract was given, then during the administration of this extract, when she exhibited the alterations which have just been described. Now when the extract was no longer given, the configuration of the electrocardiogram reverted to its earlier type, characterized by low QRS complexes and flat low T-waves. Once again when the extract was given, changes were recorded in the electrocardiograms as before.

In the case of M. S. (Case 5) who had experienced total thyroidectomy, the use of thyroid extract was associated with increase in amplitude of the T-waves and in changes in the chest lead similar to those which we have described.

The electrocardiographic characteristics of myxedema appear to be low amplitude of the QRS complexes and of the T-waves in the three standard leads, as well as in the chest lead. Moreover, the Q-waves in the chest lead are small. The administration of thyroid extract results in increase in amplitude of the QRS complexes and of the T-waves.

The nature of the cardiac enlargement [4] in the myxedematous state is not known. Whether there is dilatation of the chambers of the heart associated with altered venous return (although our observations show no significant alteration) or increase in circulating blood volume, or whether enlargement is a consequence of alterations in the muscle fibers and tissue spaces, are matters which have not been settled. Most authors agree that such a heart is microscopically very little different from normal heart muscle, although all call attention to the large, flabby organ when the gross specimen is examined.

That it is not hypertrophy of the organ is apparent since its size decreases so readily when thyroid extract is given; in short, it is a reversible reaction. Moreover, the heart in this state is a sluggish organ and accomplishes less work than normal at each beat (Table I). We have calculated the work per beat by making use of Starling's formula (19):

$$W = QR + \frac{wV^2}{2g}$$

in which W equals the work done per beat; Q equals the volume of blood expelled per beat; R equals the mean arterial blood pressure in mm. of Hg $\times$ 13.6; V equals the velocity of blood at the aorta; w equals the weight of blood; g equals acceleration due to gravity. The last part of the formula, $wV^2/2g$, has been omitted in order to make our results comparable with those of Starr, Collins, and Wood (12). By substituting values in this formula we have calculated the work of the left ventricle per beat. The work per beat done by the left ventricle was found less during the period of decreased cardiac output at low metabolic levels than later when the output was greater and the basal metabolic rate normal (Table I). We have related the work per beat to the size of the heart (Figure 7). Starr and his associates (12) have shown that the work of the left ventricle which is maintaining an adequate circulation bears a linear relationship to the size of the heart; and have defined a zone of normal circulatory function. In a similar fashion we have plotted cardiac volumes as abscissae and grammeters of work of the left ventricle per beat as ordinates (Figure 7). Three of the patients (Cases 1, 2, 4) fall outside the zone of normal circulatory function, below the line *CD*, and the fourth (Case 3) within the zone, but close to the line *CD*. In short, in 3 patients the work of the heart was not commensurate with its size. As the basal metabolic rate rose with administration of thyroid extract, all move up into the zone of normal circulatory function and closer to the best line *AB* indicating improved cardiac function.

[4] "Enlargement" is used without making a distinction between hypertrophy and dilatation.

SUMMARY

In the presence of myxedema the cardiac output per minute and per beat are diminished, the

velocity of blood flow slow, and the heart larger than normal for that individual at a time when the basal metabolic rate is low. Moreover, the work per beat is low and not commensurate with the size of the heart. With the administration of thyroid extract and the increase of the basal metabolic rate to normal levels, the cardiac output increases per minute and per beat. The velocity of the blood flow increases and the heart becomes smaller. The situation is then a reversible one. In the myxedematous state the arteriovenous oxygen difference is increased. There is present apparently a defect in the maintenance of the circulation since the circulation rate is slowed to such an extent that it is inadequate even to the decreased tissue requirements for oxygen. It has to be met by encroachment upon the arteriovenous oxygen difference. The explanation of this phenomenon is not now at hand, but it has been discussed in the light of Boothby and Rynearson's hypothesis with respect to hyperthyroidism. It has been demonstrated that the lengthening of the circulation time in myxedema bears a linear relationship to the cardiac output per minute as well as to the oxygen consumption; that the arteriovenous oxygen difference has a linear relationship to the oxygen consumption and the basal metabolic rate.

BIBLIOGRAPHY

1. Zondek, H., Das Myxödemherz. München. med. Wchnschr., 1918, **65**, 1180.
2. Assmann, H., Das Myxödemherz. München. med. Wchnschr., 1919, **66**, 9.
3. Hallock, Phillip, The heart in myxedema, with a report of two cases. Am. Heart J., 1933–34, **9**, 196.
4. Means, J. H., Circulatory disturbances in diseases of the glands of internal secretion. Endocrinology, 1925, **9**, 192.
5. Golden, J. S., and Brams, W. A., Venous pressure in thyroid dysfunction. Am. Heart J., 1933–34, **9**, 802.
6. Altschule, M. D., and Volk, M. C., The minute volume output and the work of the heart in hypothyroidism. J. Clin. Invest., 1935, **14**, 385.
7. Grollman, A., The Cardiac Output of Man in Health and Disease. C. C. Thomas, Springfield, Ill., 1932.
8. Grollman, A., Friedman, B., Clark, G., and Harrison, T. R., Studies in congestive heart failure. XXIII. A critical study of methods for determining the cardiac output in patients with cardiac disease. J. Clin. Invest., 1933, **12**, 751.
9. Taylor, F. A., Thomas, A. B., and Schleiter, H. G., A direct method for the estimation of venous blood pressure. Proc. Soc. Exper. Biol. and Med., 1930, **27**, 867.
10. Levy, R. L., The size of the heart in pneumonia. A teleroentgenographic study with observations on the effect of digitalis therapy. Arch. Int. Med., 1923, **32**, 359.
11. Bardeen, C. R., Determination of the size of the heart by means of the x-rays. Am. J. Anat., 1918, **23**, 423.
12. Starr, I., Jr., Collins, L. H., Jr., and Wood, F. C., Studies of the basal work and output of the heart in clinical conditions. J. Clin. Invest., 1933, **12**, 13.
13. Boothby, W. M., and Rynearson, E. H., Increase in circulation rate produced by exophthalmic goiter compared with that produced in normal subjects by work. Arch. Int. Med., 1935, **55**, 547.
14. Stewart, H. J., Deitrick, J. E., Crane, N. F., and Wheeler, C. H., Action of digitalis in uncompensated heart disease. Part I. In the presence of regular sinus rhythm. Part II. In the presence of auricular fibrillation (In Press, Arch. Int. Med.).
15. Stewart, H. J., Crane, N. F., and Deitrick, J. E., Studies of the circulation in pernicious anemia. J. Clin. Invest., 1937, **16**, 431.
16. Fahr, G., and Ronzone, E., Circulatory compensation for deficient oxygen carrying capacity of the blood in severe anemias. Arch. Int. Med., 1922, **29**, 331.
17. Blumgart, H. L., Gargill, S. L., and Gilligan, D. R., Studies on the velocity of blood flow. XV. The velocity of blood flow and other aspects of the circulation in patients with "primary" and secondary anemia and in two patients with polycythemia vera. J. Clin. Invest., 1931, **9**, 679.
18. Wolferth, C. C., and Wood, F. C., The electrocardiographic diagnosis of coronary occlusion by the use of chest leads. Am. J. M. Sc., 1932, **183**, 30.
19. Starling, E. H., Principles of Human Physiology. Lea and Febiger, Philadelphia, 1933, 6th ed., p. 772.