

MYOPATHY DUE TO A DEFECT IN MUSCLE GLYCOGEN BREAKDOWN.

By B. McARDLE.*

(From the Clinical Research Unit, Guy's Hospital.)

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THE energy for the contraction of muscle is largely derived from the oxidation and breakdown of glycogen, a process involving many interlinked reactions and dependent on the functional integrity of numerous enzyme systems. It is surprising, therefore, that only a few diseases are known in which a serious disturbance of muscle function is directly attributable to derangement of the carbohydrate metabolism of the muscle. This paper records what is believed to be a hitherto undescribed disorder which is characterised by a gross failure of the breakdown in muscle of glycogen to lactic acid.

The patient, George W., aged 30 years, was admitted to Guy's Hospital on 19.9.47, under the care of Dr. A. C. Hampson, who on clinical grounds diagnosed a disorder of muscle metabolism and very kindly referred him to me for further investigation. For as long as the patient could remember, light exercise of any muscle had always led to pain in the muscle and, if the exercise were continued, to weakness and stiffness. For example walking a few hundred yards, particularly if fast or uphill, provoked pain in the calves and thighs, and lifting heavy weights resulted in pain in the arms. Even chewing sometimes gave rise to pain in the masseters. The pain, at first dull and aching, increased with continued exercise, while the muscles became progressively stiffer and weaker. Usually all the symptoms rapidly disappeared on resting, but when he continued the exercise not only did the symptoms increase in severity, but they persisted longer when he was finally forced to rest. If he was gripping a heavy object, he might eventually have to drop it owing to the pain and weakness, but his fingers remained in the flexed position and it might be five to ten minutes before he could voluntarily extend the fingers fully. He had found that frequent passive extension of the fingers, though stiff and painful, shortened recovery.

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I wish to thank Mrs. B. Evans and Miss L. C. Carson who performed many of the chemical estimations.

The amount of work causing pain varied from day to day, usually for no apparent reason, but he noticed that he was worse when he had an infection or when he was feeling depressed. He knew of no other precipitating, aggravating or ameliorating factors. He thought that there had been some deterioration in the year preceding his admission, but until then there had been no consistent change in his condition.

His appetite had always been enormous but, although barely 5 feet in height, he had never at any time been stout.

The only childhood illnesses he could remember were measles and chickenpox, but his disability caused him to be absent from school for long periods, and he was eventually sent to a school for backward children.

His father died (cause unknown) when the patient, the only child, was still very young. His mother, who was still alive and well, married again and had a further seven children, all of whom are healthy. He himself married and has three normal children, all daughters, aged six months to seven years. There was no history of similar trouble in his maternal relatives, but nothing was known concerning his paternal relatives.

He was alert and very co-operative and although scarcely able to read and write, his intelligence was only a little below average. His short stature was partly due to a moderate degree of kyphosis with a slight scoliosis to the right. In other respects he was well proportioned (Plate 1). The routine examination of his nervous system revealed no abnormality. The size, power and tone of the muscles were normal, no fibrillation or fasciculation could be detected, nor could any myotonic phenomena be elicited. Reflexes were all brisk and equal, the plantar responses being flexor. No sensory loss nor any abnormality in the cranial nerves or fundi was detected. The heart was not enlarged, there were no murmurs and normal pulsation was felt in the vessels of the limbs. His blood pressure was 115/70 mm.Hg.. No abnormal physical signs were detected in the lungs or abdomen.

No radiological evidence was obtained of any abnormality of the pituitary, skull, thymus, lungs or heart, and bony calcification was normal. Serum potassium 16.2 mg. %, sodium 334 mg. %, calcium 10.4 mg. %, magnesium 2.3 mg. %, and inorganic phosphate 4.3 mg. %. R.B.C. 5,100,000 per c. mm., W.B.C. 6,000 per c. mm.. Polymorphs 56%, Eosinophils 3%, Lymphocytes 40%, Monocytes 1%. No sugar, albumin, red cells or casts were found in his urine.

METHODS.

Oxygen consumption at rest and during work was measured either with the Benedict Roth closed circuit apparatus, or by collecting the expired air in a Douglas bag and analysing it with a Haldane gas analysis apparatus. *Serum potassium* was measured by the method of Kramer and Tisdall (15), the potassium cobaltinitrite being precipitated at 0.4°C. over a period of 2.3 hours and the precipitate washed three times with ice cold water. *Serum sodium* was estimated by the method of Noyons (24) adapted for the photoelectric colorimeter, *serum calcium* by the method of Clark and Collip (7), *serum magnesium* by the method of Briggs (4), *serum and urine inorganic phosphate* by that of Fiske and Subbarow (8), *serum and urine creatine and creatinine* by that of Peters (25), and *blood sugar* using a modification of the method of Nelson (23). *Blood lactate* was estimated by the method of Barker and Summerson (2) and *blood pyruvate and total hydrazones* by that of Friedemann and Haugen (9). For these latter two determinations about 2 ml. of blood were taken rapidly without stasis into a syringe and immediately discharged into 10 ml. of ice cold 10% trichloroacetic acid and shaken. The tube containing the trichloroacetic acid was weighed before and after the addition of the blood. Values for blood lactate and pyruvate are expressed therefore in terms of mg. per 100 g. of blood. The concentration of the "neutral hydrazones" derived from non-acidic aldehydes, ketones and free trioses was obtained by subtracting the value of blood pyruvate from that of the total hydrazones.

Muscle blood flows were measured in the forearm by the venous occlusion plethysmographic method of Grant and Pearson (11). In observations in which the patient was exercised, the work usually involved (1) stepping on and off stools 6½ or 12 inches in height at a rate of 6, 12, or 24 times per minute, or (2) squeezing a sphygmomanometer bulb, the expelled air being measured in a recording spirometer, or (3) raising 2.5, 4.7 or 7.0 kg. weights by means of a gripping movement on an ergometer which measured the work done in kg. m..

RESULTS.

The Effects of Exercise.

When the patient walked fast, at first nothing abnormal was noted, but after one or two hundred yards both the swing of his arms and his stride increased and became progressively stiffer. At the same time his body became inclined forward from the hips. Respiration was faster and deeper than would normally be expected. His disability was more obvious when running upstairs as rapidly as he was able, the progressive stiffness and awkwardness of his movements being very striking. On one such occasion he was completely exhausted by climbing 75 steps at a very moderate pace. He could only crawl the last few steps and then lay panting. The muscles felt normally soft and the movements of his limbs in what was necessarily a cursory examination seemed full. His pulse rate was 160. After a minute he was able to walk the short distance to the ward, and a minute later his standing pulse rate was 122. Four minutes later his lying pulse was 90, 20 beats above his normal resting pulse. At this point it was noted that very marked ankle clonus could be elicited but no other abnormal physical signs were detected. On another occasion his standing pulse rate rose from 78 to 152 as the result of running up 90 steps in 65 seconds, falling to 84 five minutes later. The pulse rate of a normal subject climbing the stairs in the same time rose 22 beats and fell below the initial value within a minute.

Different muscles were exercised and pain, stiffness and weakness occurred in all, but it was found that the forearm muscles lent themselves most easily to more detailed observation. He exercised his forearm muscles by squeezing a sphygmomanometer bulb once every second, the expelled air being collected and measured in a recording spirometer. The effect of exercise was studied (1) with the forearm circulation free, and (2) with the circulation arrested.

(1) *Exercise of forearm muscles with a free circulation.* A normal subject was able to squeeze a sphygmomanometer bulb once every second without pain or discomfort for at least 15 minutes and by that time had pumped 22 litres of air. In G.W., however, a diffuse aching pain in the forearm usually developed after 30 to 40 seconds, when he had pumped about a litre of air into the spirometer. His squeezes then became steadily weaker, the pain became worse, and he had increasing difficulty in relaxing his flexed fingers. Complete fatigue with severe pain occurred when he had pumped about two to three litres (about 120 to 150 squeezes). At this point both active and passive extension of his fingers were painful and markedly restricted although the limitation of movement was considerably less on passive than on active extension. The third and fourth digits were more flexed than the second and fifth, and there was slight ulnar deviation of the hand. Recovery of power and relief of pain were rapid on ceasing work, but full active extension of the fingers was not possible for five to ten minutes.

(2) *Ischaemic exercise of the forearm muscles.* In these observations the patient and normal control subjects squeezed the bulb once per second after the circulation to the forearm had been arrested by a sphygmomanometer cuff on the upper arm inflated to a pressure of 200 mm.Hg..

In the normal subject pain usually occurred in the hand or forearm after pumping 1.5 to 2.0 litres of air and complete fatigue of the muscles developed after pumping 4.0 to 5.5 litres. At this point flexion and particularly extension movements of the fingers were greatly reduced but passive movements of the hand and fingers were unrestricted although painful. On release of the circulation muscular power returned rapidly but on a number of occasions in two normal controls some slight shortening of the flexor muscles was observed, as shown by inability to extend the fingers fully, together with slight ulnar deviation of the hand. The flexor muscles of the forearm seemed slightly harder than those of the other forearm and full active and passive extension of the fingers caused some pain. The shortening lasted for about five minutes. It occurred usually after the second of two periods of ischaemic work, the two work periods being separated by a one or two-minute interval with a free circulation. In both periods the exercise was continued despite pain to complete fatigue, which developed in the first period after about four minutes and in the second in about one or two minutes.

In similar observations, G.W. constantly showed marked differences. The dull aching pain developed when he had performed only about one-fifth of the work required to cause pain in the normal subjects, and fatigue rapidly followed, the amount of work he could do being only about one-sixth of the normal. The shortening of the flexor muscles and the ulnar deviation of the hand noted in the normal subjects after release of the circulation was considerably greater in G.W. A more striking difference developed if the pressure in the occluding cuff were not released for one or more minutes. On these occasions when he was no longer able to squeeze the bulb it was withdrawn from his hand and he then made gripping movements with his fingers until he was unable to move them. Then on release of the circulation, gross limitation of extension of the fingers with marked ulnar deviation of the hand was invariably present. Full active extension was not possible until about twenty minutes after the release of the cuff. The greatest and most enduring shortening of the flexor muscles was observed when he exercised the forearm muscles after the arm had been depleted of blood by an Esmarch bandage and an occluding cuff. On release of the circulation his fingers remained flexed into his palms, and full movement was not regained for over an hour.

These results were therefore strikingly different from the normal, in (a) the early onset of ischaemic pain and fatigue, both of which occurred with 10 to 20 per cent. of the normal amount of work, and (b) in the abnormal shortening of the flexor muscles following ischaemic exercise.

The production of localised swellings in muscle.

Localised swellings in muscle produced by exercise were noticed by chance following the measurement of blood flow through the forearm after exercise. Following exercise of the left arm the patient complained of pain in the forearm. The forearm was not examined when the plethysmograph was removed. He still complained of aching and 5 minutes later he said "there are a couple of carbuncles coming up on my arm." In the supinator muscle a well defined tender ridge about 5 mm. wide and high and about 4 cm. long could be felt under the skin markings left by the pressure of the flange of the plethysmograph. Forty-five minutes later the ridge was broader but flatter and softer. It was still aching and tender. These swellings could be produced at will in G.W. in two ways. Exercise of the brachioradialis muscle resulted in the appearance of a well defined ridge at the point where a steel bar pressed firmly into the muscle. More conveniently the biceps muscle was exercised to complete fatigue after a sphygmomanometer cuff had been wound round the lower half of the upper arm and inflated to a pressure of 200 mm.Hg.. On rapid removal of the cuff, a swelling was usually obvious in the distal half of the biceps muscle which appeared to increase a little in size during the ensuing minute. Occasionally a part or the whole of a swelling disappeared within five minutes but more usually it persisted for one or two hours. These usually well defined and firm swellings did not pit on pressure, and were not followed by bruising. Neither blood nor oedema fluid could be withdrawn on aspiration. They seemed therefore to be due to localised shortening of muscle similar to the generalised shortening of the forearm flexor muscles after ischaemic exercise. In normal subjects similar measures did not result in localised muscle swellings.

Infiltration of 5% Novocaine into the brachioradialis muscle when in a state of well marked shortening produced by ischaemic exercise did not influence the extent of the shortening. When infiltrated into a localised swelling produced in the biceps muscle by ischaemic exercise, the effect on the size of the swelling was equivocal.

Effects of ischaemia.

Clearly exercise and particularly ischaemic exercise had an abnormal effect on his muscles. Occlusion of the circulation for 20 minutes to an arm kept at rest led to a progressive sensory loss in time similar to that described by Lewis, Pickering and Rothschild (16); after 16 minutes' occlusion he was still able to flex and extend his fingers fully. Restoration of the circulation was followed by a well-marked reactive hyperaemia and a normal recovery of sensation and muscle power. Therefore neither the sensory nor motor nerves were abnormally sensitive to the effects of ischaemia.

Electromyographic changes in muscle.

Electromyography showed that the muscle shortening was probably due to contracture (in the physiological (10) rather than in the surgical sense,

that is, a reversible shortening of the muscle fibre unassociated with any conducted action potential in the muscle) and not to spasm.

I am indebted to Dr. G. D. Dawson and Dr. P. Merton for recording the electrical activity of the muscles and to the former for the interpretation of the records. The electromyograms shown in Fig. 1 were obtained with a fine coaxial needle electrode in the belly of the left biceps brachii. The first record taken with the muscle at rest and at the start of a voluntary contraction is completely normal.

A localised swelling, readily visible and palpable, was then produced in the left biceps by ischaemic work to complete fatigue. The needle was then inserted into the middle of the swelling and the second record shown in Fig. 1 was obtained. This shows an absence of electrical activity. With the needle still in situ the patient made a slight contraction. The third record shows the normal electrical activity resulting from this contraction. Confirmed on a subsequent occasion, the absence of electrical activity in the swellings is strong evidence in favour of the swellings being contractures.

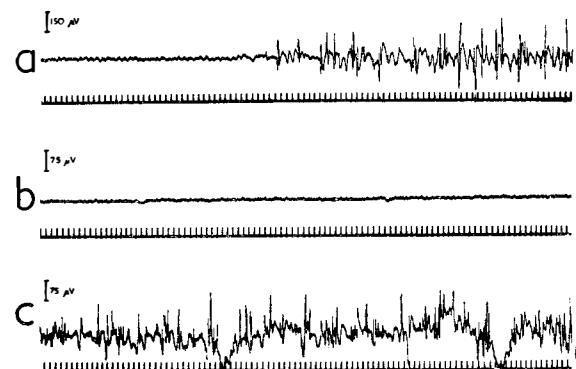


Fig. 1. Electromyograms taken with a coaxial needle electrode in the left biceps brachii of G.W.. Time marking 1/50th second peak to peak.

- (a) Muscle at rest and at start of voluntary contraction. Needle in midline of biceps.
- (b) Muscle at rest. Needle in lump produced by ischaemic exercise in the inner aspect of the biceps.
- (c) Voluntary contraction in progress. Needle as in (b) above.

Muscle blood flow.

The similarity between the pain which he experienced on exercise and the pain of intermittent claudication suggested that an inability to increase the blood flow through the exercising muscles might be partly responsible for his symptoms.

The blood flow through his right forearm was determined (a) before, during and after exercise with a full circulation, and (b) on restoration of the circulation following a period of ischaemic work. The work involved lifting a 4.76 kg. weight by a gripping movement through a distance of 3 cm. about once a second until 6.5 kg. m. of work had been accomplished. With an

unrestricted circulation the blood flow during work rose to about 20 ml. of blood per 100 ml. of forearm per minute, a normal value. At the end of work the flow rose immediately to 54 ml. per 100 ml. per minute, fell rapidly to 5.5 ml. at 3 minutes and then fell slowly to the initial resting value of 4 ml.. The values for blood flow during and after work were plotted on a graph and the area under the resulting curve was measured. This area was well within the normal limits. On the other hand, it was found that the flow following a period of ischaemic work was strikingly increased (Fig. 2), the area under the curve being 4 to 5 times that found in normal subjects performing the same amount of work. As a further comparison, two healthy male subjects exercised ischaemically to complete fatigue, and even though the work accomplished was over five times as great, the recovery blood flow of both was of the same order as that of the patient.

The abnormal blood flow following ischaemic work was not due to the 75 second period of ischaemia. Thus, a five minute period of ischaemia provoked a reactive hyperaemia a little greater than in two normal subjects. It was only about one-tenth that caused by ischaemic exercise.

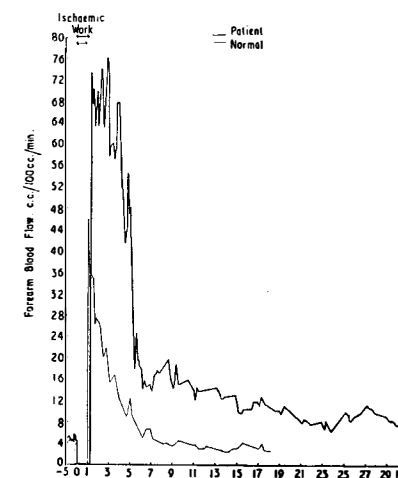


Fig. 2. The effect of ischaemic work on the blood flow through the forearm following the release of the occluding cuff in G.W. and in a normal subject. Both did 6.1 kg. m. of work on a grip ergometer.

Oxygen requirements.

Although his appetite was enormous for his size, his basal metabolic rate, estimated on two occasions, was normal (+1% and +6%). On a number of occasions his oxygen consumption was measured before, during and after differing amounts of exercise. The results are given in Table I, which also gives those on two normal subjects. As the amount of exercise increased his oxygen consumption and ventilation rate became progressively greater than the normal, particularly after the first five minutes of exercise

TABLE I.

Subject	Type of Work	Ventilation rate, litres/min./m ² .						O ₂ consumption, ml./min./m ² .						Respiratory Quotient				
		Height of steps in inches	Steps/min.	Work			Rest			Work			Rest					
				1st 5 mins.	2nd 5 mins.	3rd 5 mins.	1st 5 mins.	2nd 5 mins.	3rd 5 mins.	1st 5 mins.	2nd 5 mins.	3rd 5 mins.	1st 5 mins.				2nd 5 mins.	3rd 5 mins.
G.W. G.W.	12 12	6 6	10.0 10.8	8.2 11.0	387 391	— 538	205 295	0.905 1.01	— 538	205 295	0.892 0.91	1.19 1.05						
B.M. B.E.	12 12	6 6	8.2	5.6	378 311	380 355	192 216	0.827	380 355	192 216	0.872	1.0						
G.W. G.W.	6.5 6.5	12 12			520 500	500 510	330 275		500 510	330 275								
B.M. B.E.	6.5 6.5	12 12			460 386	496 387	209 216		496 387	209 216								
G.W. G.W.	12 12	12 12	— 10.9	9.8 11.9	— 472	925 730	335 394	0.835 0.87	925 730	335 394	0.803 0.91	0.905 0.9						
B.M. B.M.	12 12	12 12	11.0	12.3	560 545	567 555	248	0.795	567 555	248	0.885							
B.E.	12	12			470	520	248		520	248								

The ventilation rate, oxygen consumption and respiratory quotient of the patient, G.W., and of two normal controls, B.M. and B.E. during and for 5 minutes after three different levels of work.

and during the recovery period. The respiratory quotients before, during and after work were not significantly different from the normal.

The significance of these findings is not wholly clear, but it is reasonable to conclude that part at least of the increased oxygen consumption arose in overcoming the increasing stiffness of his muscles that was so striking a feature after 5 to 10 minutes of moderate exercise.

BIOCHEMICAL INVESTIGATIONS.

An underlying metabolic disorder had always been suspected, but the routine chemical analysis of his blood in the resting state provided no clue to the nature of the defect. The changes in the blood chemistry after exercise proved more interesting.

Carbohydrate metabolism.

Changes in blood lactate, pyruvate and "neutral hydrazones" following exercise. The blood lactate following stepclimbing was examined and, as shown in Tables II and V and Fig. 3, on each occasion fell instead of rising as in the normal.

In Observations 1 and 2 (Table II) the patient lay on a couch for 70 minutes prior to exercise. He then stepclimbed for eleven minutes, by which time he was clearly very fatigued and complaining of pain and stiffness of his muscles. Venous blood samples were taken at intervals before and after exercise. The results of these and similar observations on a normal control are given in Table II. In Fig. 3 the results obtained in Observation 2 are compared with those of the control subject.

The blood lactate of the control subject rose during exercise and fell subsequently, whereas that of the patient in both experiments fell, rising after two to four minutes to levels that on neither occasion was above the pre-work level. The blood pyruvate, estimated in Observation 2, also fell after exercise instead of, as usual, slightly rising. The pyruvate then gradually rose above the pre-work level to a peak twenty minutes after ceasing work. Seventeen minutes later it was still above the pre-work level.

Although it seemed highly probable that the exercising muscles were directly responsible for the fall in blood lactate, further observations were made using the technique described by Holling (14) on blood issuing directly from muscles that had been working ischaemically. The patient lay on a couch for half an hour before and during the observations. Blood was withdrawn without stasis from the right antecubital vein, a cuff around the wrist inflated to a pressure of 200 mm.Hg. preventing the admixture of blood from the hand. A cuff around the right upper arm was then inflated to 200 mm.Hg. and he worked the forearm muscles ischaemically, squeezing a sphygmomanometer bulb for 45 seconds until fatigue. The fingers were markedly flexed and pain was considerable. The arm cuff was released

TABLE II.

Obs. No.	Sub-ject	Work		Time in mins.		Blood			Serum			Urine		
		Dura-tion, mins.	Average Steps/min.	Before work	After end of work	Lactate, mg. per 100 mg.	Pyru-vate, mg. per 100 mg.	Lactate —Pyru-vate ratio	Inor-ganic phosphate mg. per 100 ml.	Crea-tine, mg. per 100 ml.	Crea-tine, mg. per 100 ml.	Period	Dura-tion of period in mins.	Ml. urine per min.
1	G.W.	11	18	40 7		10.3			3.42	1.07	1	15	0.87	
						8.2			0.65	1.14	2 500 ml. water	20	1.35	
					2	4.9			0.7	3.77	3	10	3.0	
					4½	4.0					4	22	6.9	
					6½	4.0					5	28	5.68	
					8½	6.4					6	15	2.2	
2	G.W.	11	18	38 2		6.4			3.80	1.20	7	15	4.2	
						6.7			0.5	1.16	8	20	4.25	
						6.4			0.5					
						8.1	1.06	7.6		1.36	1	15	1.07	
						7.5	1.17	6.4		1.28	2 500 ml. water	15	1.0	
						4.8	0.86	5.6			3	15	2.06	
6	G.W.	10½	18	56 30 3		5.7	1.24	4.6		1.20	4	22	5.72	
					11	1.34	5.6			5	39	4.72		
					16	6.9	1.47	4.7		1.28	6	15	1.33	
					20	7.4	1.85	4.0			7	15	2.14	
					37	7.1	1.37	5.2		1.12	8	15	4.4	
					67	5.4	1.33	4.1						
3	G.W.	10½	18	56 30 3					3.39	1.29	1	17	1.12	
									3.32	1.14	2 50 ml. water	13	1.23	
									3.34	0.9	3 50 ml. water	15	1.17	
									3.57	0.8	4 50 ml. water	15	1.8	
					36½				3.19	0.8	5 Work	12.5	1.36	
					65½				3.51	1.11	6 50 ml. water	17.5	0.86	
3	H.E.H.	11	18.5	38 2		6.7	0.72	9.3	3.24	1.11	1	15	1.1	
						4.7	0.62	7.6	2.80		2 500 ml. water	15	1.1	
					2	7.2	0.63	11.4		0.5	3	15	1.4	
					6	5.7	0.61	10.7			4	23	4.2	
					12	4.3	0.59	7.3	3.28	1.11	5	41	7.9	
					17	3.8	0.57	6.7			6	18	5.7	
3	H.E.H.	11	18.5	38 2		3.9	0.57	6.8	3.18	1.11	7	12	5.9	
						4.1	0.59	7.0			8	14	6.2	
						4.6	0.66	7.0						

2 minutes 20 seconds after inflation and the first specimen of blood withdrawn 10 seconds later. Further samples of muscle blood were taken at intervals for 25 minutes, the cuff around the wrist being inflated and the forearm veins drained before taking the sample from the antecubital vein. At the end of the experiment, that is 22½ minutes after the release of the circulation to the forearm muscles, he was still unable to extend his fingers fully, although full passive extension was possible.

Ten seconds after the release of the circulation the lactate content of blood issuing from muscles that had been working ischaemically had fallen (Observation 4, Table III and Fig. 4). This fall contrasts strongly with the rise occurring in similar observations on a normal subject. There was no fall in blood pyruvate such as occurred in the step climbing experiments, but the rise in pyruvate occurred later and was less marked than in the normal control.

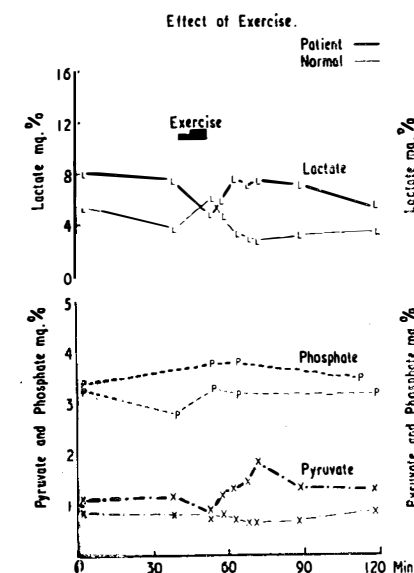


Fig. 3.

Fig. 3. Effect of exercise (stepclimbing) on the blood lactate and pyruvate and on the serum inorganic phosphate of G.W. and a normal control.

Fig. 4. Effect on the blood lactate and pyruvate and on the serum potassium and inorganic phosphate of ischaemic work of the forearm muscles. Blood was taken from the antecubital vein draining the forearm muscles of G.W. and a normal control, before and following the ischaemic work.

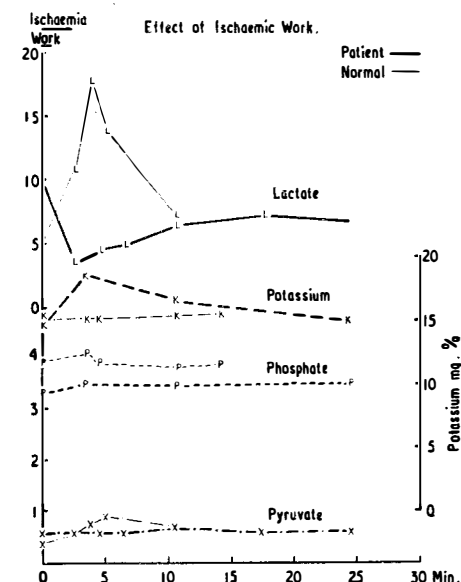


Fig. 4.

The "neutral hydrazones" in the blood (Table III, Observations 4 and 5, and Table V, Observations 7 and 8) showed no consistent trend as the result of exercise either in the blood of the patient or in the control, but it is perhaps noteworthy that on two occasions these compounds (aldehydes, ketones and free trioses) rose following exercise to above 0.9 mg. per 100 mg.. Friedemann and Haugen (9) found the range of these substances in the blood

TABLE III.

Subject	Time mins. sec.	Remarks	Lactate, mg. per 100 mg.	Pyru- vate, mg. per 100 mg.	Neutral hydra- zones, mg. per 100 mg.	Lactate —Pyru- vate ratio	K mg. per 100 ml.	PO ₄ mg. per 100 ml.	Crea- tine, mg. per 100 ml.	Crea- tine, mg. per 100 ml.
Obs. 4. G.W. Right arm	-1	Cuff inflated to 200 mm.Hg. Work started. Fatigued, and considerable pain. Work stopped, 1.3 litres of air pumped. Cuff released.	9.8	0.56	0.81	17.5	14.8	3.33	0.7	1.25
	0									
	0.45									
	2.20		3.7	0.62	0.87	6.0				
	2.30		4.6	0.61	0.86	7.5	18.6	3.51	0.56	1.34
	3.15		5.1	0.59	0.76	8.6				
	4.30		6.6	0.72	0.71	9.2	16.6	3.49	1.0	1.2
	6.30		7.3	0.62	0.68	11.8				
	10.30		6.8	0.64	0.98	10.6	15.1	3.58	1.82	1.28
	17.30		6.1	0.58	0.79	10.5	16.2	3.59	0.9	1.34
Obs. 5. B.M. Left arm	0	Cuff inflated to 200 mm.Hg. Work started. Work stopped. No pain or fatigue. 1.3 litres of air pumped. Cuff released.	5.4	0.41	0.42	13.2	15.1	3.98		
	0.45									
	2.20		11.1	0.55	0.33	20.2	15.3	4.17		
	2.30		17.8	0.76	0.55	23.4	15.3	3.95		
	3.20									
	3.45									
	4.20		14.0	0.92	0.35	15.2	15.5	3.88		
	5.00		7.2	0.71	0.21	10.1	15.6	3.95		
	10.30									
	14.00									

Changes in lactate, pyruvate and other substances in blood issuing from the forearm muscles of G.W. and a normal control, B.M., following the release of the circulation after ischaemic work.

of 40 resting normals to be from 0.1 to 0.7 mg. per 100 mg., and they did not find any significant increase with exercise. Nor has such a rise been encountered in a large number of observations made mainly on one normal subject after varying grades of exercise.

Changes in other blood constituents. Whereas the blood lactate showed an abnormal fall after exercise, the serum potassium rose in Observation 4 from 14.8 to 18.6 mg. per 100 ml. immediately after exercise and was still 16.6 mg. per 100 ml. eight minutes later, in contrast to the control observation in which there was no significant change. The rise in potassium was of the same order as that seen when the control subject worked ischaemically to complete fatigue of the muscles, performing about four times as much work as did the patient. Although both patient and control showed the same small rise in inorganic phosphate, it should be remembered that the blood flow in the patient was probably considerably greater than in the control. It follows, if this were the case, that the loss of phosphate was greater in the patient than in the control. Observation 6, Table II, carried out in exactly the same way as Observations 1 and 2, was performed to investigate the creatine-creatinine metabolism. The serum creatinine did not change significantly in this or any of the experiments in which it was determined but further investigation will be necessary before the creatine findings can be satisfactorily interpreted. The blood creatine has usually been above the renal threshold of 0.5 mg. % (28, 31), yet creatine was not ordinarily found in his urine, and then only in amounts within the experimental error of the method. Since the endogenous creatinine clearance was within normal limits, this would suggest therefore that there was increased tubular reabsorption of creatine (31). The highest creatine levels were observed in blood coming from muscles that had been working ischaemically, some minutes after restoration of the circulation. This suggests release of creatine from the muscles during this phase of recovery, but the mechanism underlying the release is obscure.

Changes following adrenaline. It was clear that during exercise there was a gross defect in the breakdown of glycogen to lactic acid in the muscles. Two experiments were therefore performed to determine if a similar defect existed during glycogenolysis induced by adrenaline. The experiments were similar except that in the first observation the adrenaline, 0.7 ml. of a 1/1,000 solution (*i.e.*, 0.5 mg./sq. metre) was given subcutaneously and in the second intramuscularly. The patient lay on a couch for half an hour before and during the procedure. No significant difference in the blood changes following the adrenaline between the two experiments was observed. The changes on the second occasion are shown in Fig. 5, the findings of a similar observation using the same adrenaline solution on a normal control being included for comparison. Following the injection, although the pulse rate remained steady, the systolic blood pressure rose over a period of twenty-five minutes from 115 to 135 mm.Hg. and remained at this level for half an hour,

falling to 125 mm. one hundred and ten minutes after the injection. The usual subjective sensations of tremulousness and forcible heart beat were noted by the patient. The rise in both venous and arterial blood sugar was within normal limits, but the venous blood sugars have been omitted for clarity from Fig. 4. This together with the subjective symptoms indicate that the adrenaline was absorbed normally. On the other hand the rise in blood lactate and pyruvate was slower and less than half that of the normal shown in Fig. 5. The change in inorganic phosphate was also small; that of the patient falling 0.3 mg. per 100 mg. as compared with 1.0 mg. per 100 mg. in the normal control. The fall in potassium although less abrupt than that of the control and followed by a slower rise was within normal limits (6). The "neutral hydrazones" were unchanged. The rise in lactate and pyruvate showed that some glycolysis was taking place following adrenaline, but it was clearly less than that of the normal subject C, and it was also considerably less than that of two other normals whose results are not included in this paper.

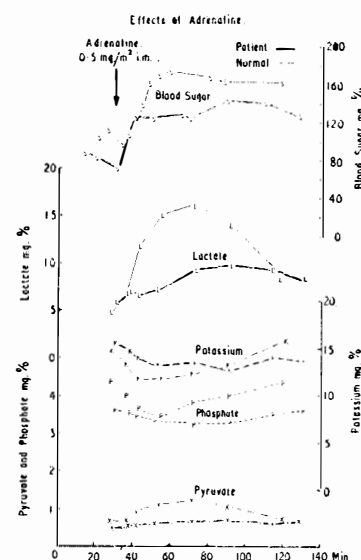


Fig. 5. Effects of adrenaline 0.5 mg./sq. metre/min. intramuscularly on the blood sugar, lactate and pyruvate and on the serum potassium and inorganic phosphate of G.W. and a normal control.

Glycolysis in shed blood. It remained to be seen whether the glycolysis that normally occurs in shed blood could also occur in that of the patient. A blood sample was rapidly drawn without stasis through a wide bore needle and of this about 2 ml. were immediately deproteinised, the exact amount being determined by subsequent weighing. The remaining 18 ml. of blood was put in a flask containing heparin and placed in an incubator maintained

at 37°C.. Specimens were withdrawn at intervals for three hours, and analysed for lactate, pyruvates and "neutral hydrazones." The results are given in Table IV.

The accumulation of lactic acid on incubation shows that glycolysis is occurring in the blood. The rate of formation of the lactic acid was the same as that found in the incubated blood of eight normal controls and of the same order as that found by Bird (3). The initial fall in the blood pyruvate followed by a rise in the second and third hours was also similar to that found in the blood of the eight normal controls, and agrees with the findings of Wilkins, Weiss and Taylor (29) and of Bueding and Wortis (5).

TABLE IV.

Showing the normal changes in lactate, pyruvate and "neutral hydrazones" occurring on incubating the shed blood of G.W. at 37°C.

Time from withdrawal of blood	Lactate, mg. %	Pyruvate, mg. %	"Neutral hydrazones," mg. %
$\frac{1}{2}$ min.	3.3	0.58	0.59
30 mins.	6.7	0.48	0.52
1 hour	11.6	0.44	0.59
2 hours	36.4	0.58	0.56
3 hours	56.5	0.77	0.42

Changes in urine.

Exercise normally inhibits the diuresis that follows the ingestion of 500 ml. of water, the extent of the suppression being dependent on the duration and intensity of the exercise (12). On a number of occasions it was observed following the ingestion of 500 ml. of water that an amount of exercise that in the normal had little effect on the subsequent water diuresis, produced a material inhibition of the urinary flow of the patient. Thus in Observations 1 and 2 (Table II) the degree of inhibition is markedly greater in the patient than in the normal control subject (Observation 3). Phosphate and endogenous creatinine clearances showed no significant departure from the normal. Creatine was not found in significant amounts in the urine either at rest or after work.

The action of various drugs.

(1) *The action of B.A.L.* Lundsgaard in 1930 (17, 18) showed that frog muscle poisoned with sodium iodoacetate when stimulated contracted normally for a short time before going into a contracture (13). The main significance of the work lay in the fact that the contractions of the poisoned muscle, even under anaerobic conditions, occurred without the formation of any lactic acid. As it was shown that glycogen was broken down in the muscles it was clear that glycogenolysis was incomplete. The marked similarity between the clinical, biochemical and electromyographic findings

in G.W. and the behaviour of iodoacetate poisoned muscle is evident. Bacq (1) has found that muscles poisoned by vesicant gases or by immersion in solutions of heavy metals behave in an exactly similar fashion to those poisoned with iodoacetate, and he suggested that these substances acted on the sulphhydryl containing enzymes in muscle. As the result of the work of Peters, Stocken and Thompson (26) it is now well known that B.A.L. reverses the toxic action of arsenic and certain heavy metals. It seemed possible therefore that B.A.L. might have a similar effect on the muscles of the patient. Accordingly the patient was given 225 mg. of B.A.L. intramuscularly in three doses of 75 mg. at three hour intervals. Muscle function was judged on a grip ergometer and on his ability to climb stairs. For an hour after the first injection there was no improvement on the control figures, but there was then a rapid improvement which was maintained throughout the day and which the patient considered lasted for another twenty-four hours. A further trial was made, and unknown to the patient an injection of saline was given intramuscularly one hour before the injection of B.A.L.. Following the saline injection there was a marked but transient improvement in muscle function. At this point 150 mg. of B.A.L. was injected intramuscularly. Following this injection his performance deteriorated and forty-five minutes later was worse than the initial efforts. Fifteen minutes later, that is one hour after the B.A.L., at a time when he was feeling depressed at the apparent failure of the B.A.L., there was a striking improvement which persisted for the ensuing hour and a half during which tests were performed. The effect of B.A.L. on his ability to form lactate and pyruvate during exercise was also determined. Ninety minutes

TABLE V.

Observation No.	Work		Time in mins.		Blood			
	Duration, mins.	Average steps per min.	Before work	At end of work	Lactate, mg. per 100 mg.	Pyruvate, mg. per 100 mg.	"Neutral hydrazones," mg. per 100 mg.	Lactate—Pyruvate ratio
7	7	21.3	1		8.7	1.99	0.38	8.0
				$\frac{1}{4}$	6.5	0.86	0.51	7.6
				$1\frac{1}{4}$	8.3	0.87	0.91	9.5
8	10	24.3	1		10.6	1.24	0.50	8.6
				$\frac{1}{4}$	6.9	1.15	0.41	6.0
				$1\frac{1}{4}$	6.0	1.24	0.50	4.9

Changes in blood lactate, pyruvate and "neutral hydrazones" of G.W. following exercise (stepclimbing). B.A.L. 150 mg. intramuscularly was given 90 minutes after Observation 7 and 120 minutes before Observation 8.

before the injection of B.A.L. blood was taken from an arm vein immediately before work involving stepping on and off a 1 foot stool, 24 steps per minute. He could not keep to this rate and after 7 minutes was unable to continue, his average rate of stepping being 21.3 steps per minute. Blood was withdrawn fifteen seconds after ceasing work and again one minute later. Two hours after the injection of the 150 mg. of B.A.L. at a time when the improvement was at its height, the test was repeated, but this time he was able to complete the 10 minute period of exercise with ease at an average rate of 24.3 steps per minute. Blood was withdrawn before and after the exercise as before. Table V shows that the blood lactate fell after exercise on both occasions.

(2) *Effect of other drugs.* A number of drugs was tried, usually on an entirely empirical basis. None led to any significant improvement either subjectively or as shown by his performance on a grip ergometer, with the possible exception of calcium gluconate which, when given intravenously (10 ml. of a 10% solution), led to a small and very transient improvement. Adrenaline 0.25 mg. subcutaneously, prostigmine 1 mg. with atropine 0.6 mg. subcutaneously, and potassium chloride 3 g. by mouth were without effect either on the pain or on the weakness. Definite deterioration followed two hours after taking quinine sulphate 0.65 g. by mouth. Riboflavine 1 mg. t.d.s., nicotinic acid 100 mg. t.d.s. and tocopherol 40 mg. t.d.s. were each tried separately for 2-4 weeks without any effect. Methionine 2 g. was given daily for a fortnight but failed to produce any improvement.

DISCUSSION.

The clinical picture presented by this patient does not seem to correspond with any disorder of muscle hitherto described. It most closely resembles the rare and rather ill-defined disease hypertrophia musculorum vera. According to Woods (30) this disease is very slowly progressive, occurs predominantly in males, and is characterised by weakness and easy fatigue of single muscles or groups of muscles particularly of the upper extremity. Pain or aching in the muscles may occur. The weakness of the muscles is in marked contrast to their increased bulk. Tendon reflexes, mechanical irritability and electrical reactions are little or not at all affected. Histologically the individual muscle fibres show hypertrophy with some increase in nuclei, but without evidence of degeneration or increase in fibrous or fatty tissue. Pain on exertion does not appear to be a prominent feature and the stiffness and contractures of the muscle which have been so striking in G.W. are not mentioned, although in the case of hypertrophia musculorum vera described by Woods muscular cramps occurred at rest associated with the apparently spontaneous, momentary appearance of hard rounded tumours in his muscles. A case of hypertrophia musculorum vera described by Maxwell (20) bears a rather closer resemblance to G.W., in that exertion led both to cramp-like pains and to weakness of the muscles of the lower

limbs. Certain differences however, exist between the two cases. In the patient described by Maxwell symptoms did not occur until the age of 15 years. The occurrence of muscular stiffness during exercise is not mentioned, and marked hypertrophy was present of the quadriceps femoris, the glutei and of the muscles of the calves and forearms. A histological examination of muscle from G.W. has not been done, but there is no clinical evidence of either hypertrophy or atrophy of his muscles. Biochemical investigations on cases of hypertrophia musculorum vera have been meagre, but the case described by Maxwell had a conspicuous creatinuria in contrast to G.W. whose urine did not contain creatine. It seems clear therefore that although the condition from which G.W. is suffering may have some affinity with hypertrophia musculorum vera it is distinct from it.

The lack of stiffness at the onset of exercise, and the striking effect of ischaemic exercise in provoking the pain and stiffness is strong evidence against Thomsen's disease, a condition which is also ruled out by the biochemical and electromyographic findings, and by the failure to respond to quinine. That the condition was not hysterical or functional was clearly shown by the localised swellings in the muscles, by the blood flow, biochemical and electromyographic findings, and by the personality of the patient which was quite unlike that found in purely functional disorders.

The abnormally rapid onset of pain, weakness and stiffness and the shortening of muscle during and after ischaemic work all point strongly to the peripheral site of the lesion. The normal electromyogram during muscle contraction together with the inability to obtain any demonstrable action potentials from the localised muscular swellings in the absence of voluntary contraction strongly suggest an abnormality of the muscle fibres rather than of the peripheral nerves or nerve endings. It is legitimate as the result of the electromyographic findings to regard both the localised muscle swellings and the shortening of the muscle as a whole as due to contractures (in the physiological sense as defined by Gasser (10)) with the qualification that better methods of recording electrical changes in the muscle may yet render this suggestion untenable. The view that the muscle shortening is a contracture is further supported by the close resemblance to the effects produced by poisoning skeletal muscle with iodoacetate. Lundsgaard (17, 18) showed that skeletal muscle poisoned with iodoacetate when stimulated is able to contract normally for a short time, but it then fatigues rapidly, shortens and passes into contracture, an oxygenated muscle usually surviving longer than one stimulated anaerobically. Lundsgaard also demonstrated that the muscle was able to contract without the production of lactic acid, although glycogen was broken down as shown by a well marked decrease in the muscle glycogen and the accumulation of hexose monophosphates. Although Mawson (19) did not find that the lactate content of iodoacetate poisoned muscle in contracture was reduced as compared with resting control muscles, he was able to show that iodoacetate

poisoned muscles in the presence of oxygen and lactate will continue to contract long after a similar muscle without added lactate has fatigued and passed into contracture. He showed moreover that under these circumstances lactate disappeared from the perfusing fluid. It is clear that there is a close similarity between the behaviour of the iodoacetate poisoned muscles of the frog when stimulated and those of this patient when exercised. Both contract normally for a short time, fatigue quickly especially under anaerobic conditions, and pass into a contracture. Both are unable to form lactic acid even when exercising ischaemically but on the contrary can absorb and presumably utilise lactate from the fluid or blood bathing the muscle. This resemblance is increased by Somogyi and Verzar's observation (27) that iodoacetate poisoned frog muscles before the development of the contracture lost potassium when stimulated. When the contracture had developed the muscles continued to lose potassium although no longer stimulated. They linked the potassium changes with glycogen breakdown to hexose phosphate. There are only two points of difference. Somogyi and Verzar found that the amount of potassium liberated from the poisoned muscles is of the same order as that lost from normal muscles doing the same amount of work. On the other hand it would seem as though the amount of potassium lost from the muscles of the patient as judged by the rise in the serum potassium of blood coming from previously exercised ischaemic muscles, was considerably larger than that lost from normal muscles performing the same amount of ischaemic work.

The second difference, that the iodoacetate induced contracture is irreversible whereas the contractures in G.W. are clearly reversible, does not affect the main thesis that in both conditions it is the same enzyme system that is at fault. For example, the fault in the enzyme or other component of the enzyme system might be partial, or might be wholly or partly reversible in the presence of an adequate blood supply.

It seems, therefore, that the patient has a disorder of carbohydrate metabolism affecting chiefly if not entirely the skeletal muscles. The normal hyperglycaemic response to adrenaline indicates that the glycogen in the liver can be readily broken down to glucose, and the normal resting blood lactate and the normal glycolysis to lactic acid on incubation of his shed blood shows that the defect does not extend to the blood cells. The lactate and pyruvate response to adrenaline indicates also that the biochemical lesion in the muscle is a partial one. Why adrenaline should be able to lead to the production of lactic acid and pyruvic acid and exercise be unable to do so is difficult to understand unless it is assumed that during exercise any lactate produced was immediately utilised in the same manner as that abstracted from the blood stream, or that during exercise a change took place in the muscle chemistry which effectively led to a breakdown in glycogenolysis.

It has been shown by Meyerhof and Kiessling (21, 22) that, in the iodoacetate poisoned muscle, glycogen breakdown proceeds normally as far as the formation of glyceraldehyde phosphate, but that glyceraldehyde phosphate dehydrogenase, the enzyme responsible for its further breakdown to diphosphoglyceric acid, is poisoned. Theoretically, the phenomena following iodoacetate poisoning of this enzyme could also be caused by interference with the other components of the enzyme system. It is suggested therefore that it is the glyceraldehyde phosphate dehydrogenase system that is the site of the biochemical lesion in the muscles of G.W..

SUMMARY.

1. A case is described of a man who had suffered all his life from muscular pain, weakness and stiffness following slight exertion. Ischæmic exercise of a limb gave rise to a very rapid appearance of these symptoms and to gross shortening of the exercised muscles. Exercise of a muscle, a portion of which had been rendered ischæmic, resulted in shortening of the ischæmic portion of the muscle, manifested as a visible and palpable swelling. Such swellings persisted up to two or more hours after release of the circulation.

2. In contrast to the normal, the blood lactate fell during exercise (stepclimbing). The blood pyruvate also fell during exercise but on resting rose to an abnormally high level several minutes after ceasing work.

3. The same fall in blood lactate and an abnormal rise in serum potassium was observed in the blood issuing from forearm muscles previously exercised ischæmically.

4. The muscle blood flow following ischæmic exercise was about five times greater than normal.

5. The blood lactate and pyruvate rose following the intramuscular injection of adrenaline 0.5 mg./sq. metre, but the rise was considerably lower than that found in normal controls.

6. Electromyograms recorded with a needle in a muscle swelling produced by ischæmic exercise showed an absence of any action potentials except during voluntary effort.

7. It is suggested that the shortening of the muscles observed after ischæmic work was due to the development of contractures resulting from the inability of the muscles to break down glycogen to lactic acid. The essential similarity is indicated between the findings in this case and those observed in muscles poisoned with iodoacetate or heavy metals and it is suggested that the biochemical lesion may be similar.

REFERENCES.

- (1) BACQ. Bull. acad. roy. Med. Belg., 1942, **7**, 108.
- (2) BARKER AND SUMMERSON. J. biol. Chem., 1941, **138**, 535.
- (3) BIRD. J. biol. Chem., 1947, **169**, 493.
- (4) BRIGGS. J. biol. Chem., 1922, **52**, 349.
- (5) BUEIDING AND WORTIS. J. biol. Chem., 1940, **133**, 585.
- (6) CASTLEDEN. Clin. Sci., 1938, **3**, 241.
- (7) CLARK AND COLLIP. J. biol. Chem., 1925, **63**, 461.
- (8) FISKE AND SUBBAROW. J. biol. Chem., 1925, **66**, 375.
- (9) FRIEDEMANN AND HAUGEN. J. biol. Chem., 1943, **147**, 417.
- (10) GASSER. Physiol. Rev., 1930, **10**, 35.
- (11) GRANT AND PEARSON. Clin. Sci., 1938, **3**, 119.
- (12) HELLEBRANDT, WALTERS AND MILLER. Amer. J. Physiol., 1936, **116**, 168.
- (13) HENRIQUES AND LUNDGAARD. Biochem. Z., 1931, **236**, 219.
- (14) HOLLING. Clin. Sci., 1939, **4**, 103.
- (15) KRAMER AND TISDALL. J. biol. Chem., 1921, **46**, 339.
- (16) LEWIS, PICKERING AND ROTHSCILD. Heart, 1931, **16**, 1.
- (17) LUNDGAARD. Biochem. Z., 1930, **217**, 162.
- (18) LUNDGAARD. Biochem. Z., 1930, **227**, 51.
- (19) MAWSON. J. Physiol., 1932, **75**, 201.
- (20) MAXWELL. Brit. med. J., 1947, **2**, 656.
- (21) MEYERHOF AND KIESSLING. Biochem. Z., 1933, **264**, 40.
- (22) MEYERHOF AND KIESSLING. Biochem. Z., 1933, **267**, 313.
- (23) NELSON. J. biol. Chem., 1944, **153**, 375.
- (24) NOYONS. Pharm. Weekbl., 1939, **76**, 307. Quoted by King. "Micro-analysis in Medical Biochemistry," Churchill, London, 1946.
- (25) PETERS. J. biol. Chem., 1942, **146**, 179.
- (26) PETERS, STOCKEN AND THOMPSON. Nature, Lond., 1945, **156**, 616.
- (27) SOMOGYI AND VERZAR. Helv. med. Acta, 1941, Suppl. No. 6, **7**, 81.
- (28) TIERNEY AND PETERS. J. clin. Invest., 1943, **22**, 595.
- (29) WILKINS, WEISS AND TAYLOR. Proc. Soc. exp. Biol., N.Y., 1938, **38**, 296.
- (30) WOODS. J. nerv. ment. Dis., 1911, **38**, 532.
- (31) ZIERLER, FOLK, MAGLADERY AND LILLIENTHAL. Bull. Johns Hopkins Hosp., 1949, **85**, 370.

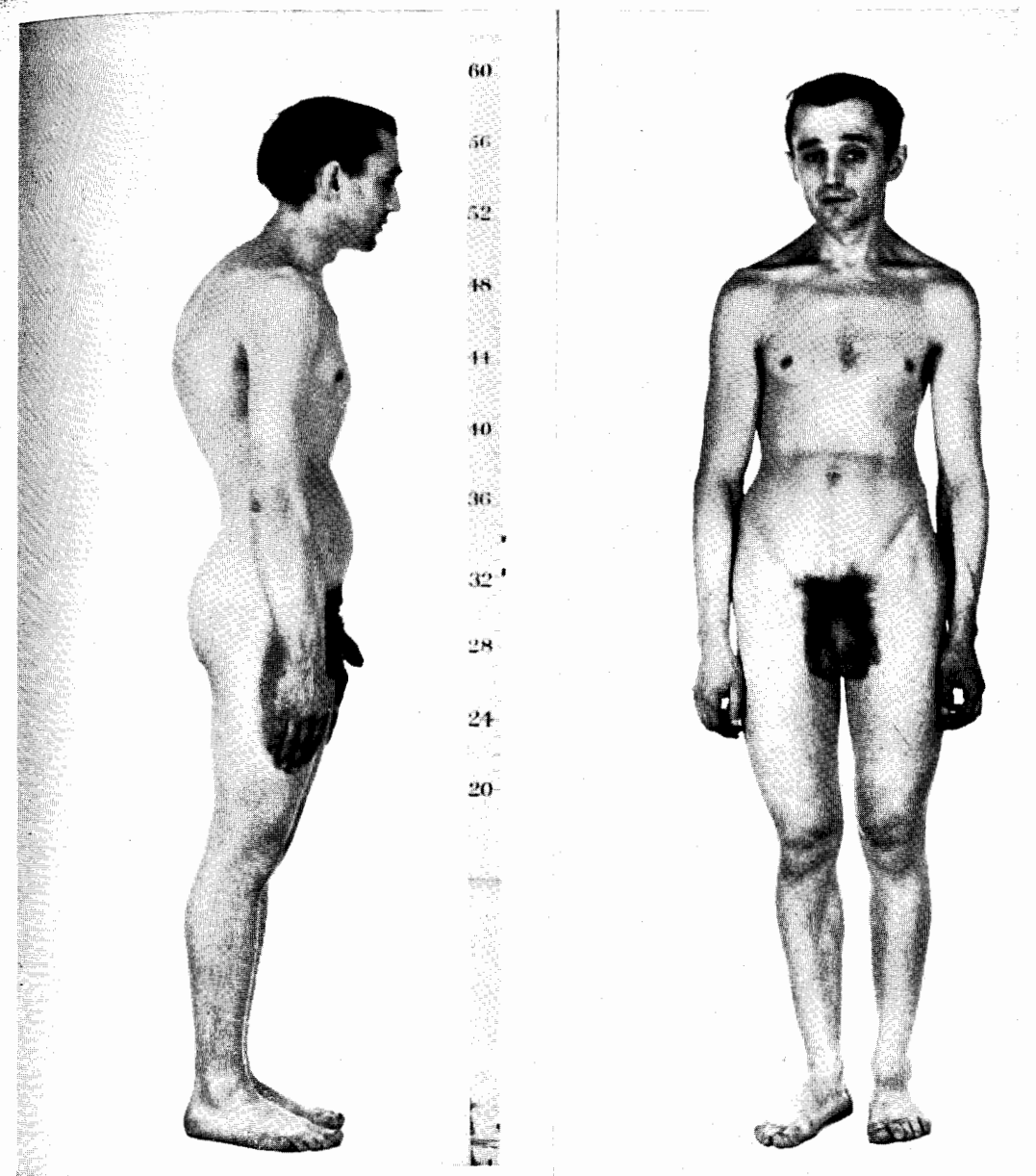


Plate 1. G.W., aged 30. Apart from the short stature and the kyphosis, the musculature and body development are quite normal.