Studies on the Effect of Muscular Exercise in Beri-beri.

Third Report.

The Oxygen Debt, Oxygen Requirement and the Changes in RQ, Respiratory Volume and CO₂ Output through Muscular Exercise.

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I. INTRODUCTION.

In the first report, finding a disturbance in lactic acid metabolism during muscular exercise in beri-beri, we¹⁾ explained with it the augmentation in gastrocnemius muscle expansion observed after the exercise, as the delayed resynthesis of lactic acid, that is formed through muscular exercise, should deteriorate the acidotic condition. In efforts to attribute also to this resynthetic disorder in lactic acid that in beri-beri patient the oxygen intake increased by muscle work does not easily return to the original value

1) Inawashiro and Hayasaka, Tohoku Journ. Exp. Med., 1928, 12, 1.

at rest, we ascertained it from various factors and presumed thereby the oxygen debt to be much augmented. Further we communicated that although the oxygen intake during the exercise was apt to be larger in the acme than after its recovery, we could not put on to this fact any special significance unless the oxygen requirement was estimated.

For this reason, in the present communication we intend to throw clear light on the entity of fatigue in beri-beri, accurately observing the recovery from the state of fatigue due to muscular exercise by estimating oxygen debt and oxygen requirement and furthermore by investigating the lactic acid accumulation in muscles.

It has been well noticed in the past that the gaseous exchange increased by muscle work in healthy man continues for a short time after the cessation of the muscular exercise (Vierordt,²⁾ Smith,³⁾ Speck,⁴⁾ Benedict and Cathcart.⁵⁾ Smith³⁾ named this phenomenon "After effect of work," and Durig and Zuntz⁶⁾ also called it "Nachwirkung von Arbeit." Barcroft and Kato⁷⁾ proved the same fact, precisely estimating the oxygen intake and blood flow in gastrocnemius muscles of dogs during and after excitement. Hill and Lupton,⁸⁾ after carefully studying this phenomenon, introduced the word "oxygen debt and oxygen requirement." As Meyerhof⁹⁾ has already elucidated, muscular contraction is brought about by the energy which is produced by conversion of glycogen into lactic acid under anaerobic condition, and in the convalescent process of the contraction a part of the lactic acid is oxidized, the remainder being again synthesized into glycogen. For this reason, excessive oxygen is demanded for the convalescent state, but the convalescent process, already taking place during exercise, gives rise to a much increased oxygen intake, which continues for a short time even after the cessation of the exercise, if it exceeds the limit of respiratory and circulatory activity capable of supplying oxygen needed in every moment. The total sum of the excessive oxygen consumption after the cessation of the exercise is called the oxygen debt and it is spent for re-synthesis of the lactic acid retained in the body for a moment after the cessation of the exercise. According to Hill's⁸⁾ calculation, only 5% of the

2) Vierordt, Cited by Campbell, Proc. Roy. Soc. London 1925, **97**, 43.

3) Smith, Ibid.

4) Speck, Ibid.

5) Benedict and Cathcart, Ibid.

6) Durig and Zuntz, Skand. Arch. f. Physiol., 1913, **29**, 133.

7) Barcroft and Kato, Phil. Trans. Roy. Soc. London, 1915, B, **207**, 149.

8) Hill and Lupton, Journ. Physiol. 1922, **56**, 32.

9) Meyerhof, Pflüger's Arch., 1921, **191**, 128.

oxygen debt is responsible for the extra action of circulatory and respiratory apparatus.

II. METHOD OF EXPERIMENTS.

We carried out the experiments according to Hill ; that is, we caught the exhaled air in an air-tight bag, the volume of which was measured by Boothby's tank. A part of the exhaled air was analyzed with especially detailed attention. The rubber bags were of three sorts :—of 30, 60 & 200 litres content. We selected beri-beri patients with typical symptoms, particularly circulatory failure, as examinees. The examinees were determined early in the morning when the stomachs were empty, 14–16 hours after their previous supper, first of all of the gaseous metabolism at rest, and then during exercise which consists in running on tread-mill for five minutes, as well as afterwards for 60–90 minutes, namely, twice every $2\frac{1}{2}$ minutes during the exercise and also twice every $2\frac{1}{2}$ minutes after the exercise, further thrice every 5 minutes thereafter, and several more times at intervals of 10–20 minutes.

We observed in the course of 60–90 minutes the total amount of the extra oxygen consumption, obtained by subtracting the oxygen consumption at rest from that after the cessation of the exercise, which we regarded as oxygen debt. Since the oxygen consumption augmented by muscular exercise, however, occasionally does not return to the resting value even after 90 minutes, the real value in oxygen debt may be larger than that here obtained. Adding the oxygen debt to the extra oxygen consumption during the muscular exercise, we calculated the oxygen requirement. Furthermore, in continuously noting the respiratory volume per minute, CO_2 content in expirium, its output per minute, and RQ at rest, during the muscular exercise and during the recovery, we investigated the acidotic change before and after the exercise.

The examinees numbered altogether 8 beri-beri patients with typical symptoms, especially with remarkable circulatory findings, among whom 5 cases were again similarly examined upon their recuperation, in order to compare the results after recovery with those in the acme of the disease.

III. RESULTS OF EXPERIMENTS.

A. *Oxygen Debt.*

We see that the oxygen intake during the muscular work in any case

of beri-beri in its acme is obviously larger, as contrasted with that in its recovery, and this is also true during the period of recovering from muscular exercise (Table I & Fig. 1). In the cases of the patients recovered from beri-beri the increased oxygen consumption through muscular exercise is approximately resumed within 10 minutes after the exercise, perfectly returning to the value at rest within 1 hour, while in the majority

TABLE I.

O₂ requirement and O₂ debt in beri-beri and after its recovery.

No.	Subject	Sex	Age	Acme			Recovery		
				O ₂ require- ment (c.c.)	O ₂ debt (c.c.)	$\frac{\text{O}_2 \text{ debt}}{\text{O}_2 \text{ req.}} \times 100$	O ₂ require- ment (c.c.)	O ₂ debt (c.c.)	$\frac{\text{O}_2 \text{ debt}}{\text{O}_2 \text{ req.}} \times 100$
1	T. N.	M.	20	7720	3950	51.2	4250	875	20.6
2	S. K.	"	29	4413	1288	29.2	3000	413	13.8
3	S. S.	"	18	7538	5325	70.6	4562	1100	24.1
4	T. N.	"	18	7125	4000	56.1	2400	350	14.6
5	M. K.	"	15	9228	5576	60.4	3652	651	17.8
6	K. S.	"	17	9075	5875	64.7	3788	1064	28.1
7	I. S.	"	19	5623	2323	41.3			
8	M. G.	"	22	6388	3038	47.6			
Average				7139	3922	52.6	3609	742	19.8

Fig. 1.

Case 5. O₂ requirement and O₂ debt in the acme of beri-beri (dotted line) and its recovery (substantial line).

of beri-beri patients in the acme it is not restored completely even 60-90 minutes after the exercise. This is in accord with what was said in our first report. For this reason, without getting the complete value in oxygen debt, we obtained only the approximate figure.

As was presumed in the first report, the oxygen debt has turned out to be considerably larger in the acme of beri-beri than in its recovery, so that in the former it is 1288 to 5875 c.c., with an average 428% above that in the recovery (Table I). In the acme of beri-beri the ratio of oxygen debt to the oxygen requirement is likewise very large. Eppinger¹⁰⁾ also found the oxygen debt to be augmented in uncompensated heart failure, but the degree in the increased oxygen debt can not be compared directly with that in our data above obtained, for the duration and grade of the muscular exercise is not similar.

Since the oxygen debt is usually spent for burning of lactic acid accumulated after the cessation of muscular exercise, the acid content retained in body at the moment can be reckoned indirectly from this.

Furthermore, the acid content accumulated in the acting muscles themselves at this moment can be calculated. The calculation is based on the fact that about 7 grms. of lactic acid so formed may be oxidized by 1 litre of oxygen and that one fifth of the lactic acid is burnt, the remainder being again synthesized into glycogen. According to Hill⁹⁾ the muscles acting during walking correspond to 30% of the body weight, because the muscles in body occupy in general 40% of the body weight, among which the muscles working during walking are said to amount to 75%. In this manner the lactic acid accumulated in muscles can be calculated. Since the lactic acid contained in the muscles streams into blood and lymph or is diffused to the surrounding tissues, the acid really contained in muscles may amount to about $\frac{2}{3}$ of the figure shown in Table II.

As is shown in this Table, in the recovery of beri-beri the lactic acid content in muscles after the cessation of exercise is only from 0.015 to 0.054%, on an average 0.034%, while in its acme it amounts to from 0.049 to 0.226% with an average 0.178%, that is, the lactic acid accumulated in muscles at the moment after the suspension of exercise is obviously plentiful.

In stimulating frog muscle until it reaches extreme fatigue, Meyerhof⁹⁾ estimated the lactic acid content in the muscles, which showed 0.35% as a maximum value, and presumed that a greater value should be attained

10) Eppinger, *Das Versagen des Kreislaufes*, Berlin 1927.

TABLE II.

Effect of muscular exercise on lactic acid metabolism in beri-beri and after its recovery.

No.	Subject	Sex	Age	In acme						After recovery				
				Body weight (kilos)	O ₂ requirement (c.c.)	Total lactic acid in Body (grms.)	Lactic acid per kilo body weight (grms.)	Lactic acid in muscle (%)		Body weight (kilos)	O ₂ requirement (c.c.)	Total lactic acid in Body (grms.)	Lactic acid per kilo body weight (grms.)	Lactic acid in muscle (%)
1	T. N.	M.	20	63.50	7720	27.65	0.435	0.145		61.05	4250	6.13	0.101	0.034
2	S. K.	"	19	60.25	4413	9.02	0.149	0.050		54.25	3000	2.89	0.053	0.018
3	S. K.	"	18	57.60	5325	37.23	0.047	0.216		53.70	4562	7.70	0.143	0.048
4	T. N.	"	18	56.45	4000	28.00	0.436	0.165		53.40	2400	2.45	0.046	0.015
5	M. K.	"	15	47.20	9228	39.03	0.827	0.276		40.95	3632	4.56	0.111	0.037
6	K. S.	"	17	50.50	9075	41.13	0.814	0.271		45.75	3788	7.45	0.163	0.054
7	I. S.	"	19	41.20	5623	16.26	0.395	0.132						
8	M. G.	"	22	42.50	6388	21.27	0.497	0.106						
Average					7139	27.46	0.533	0.178			3609	5.20	0.103	0.034

if this determination were carried out in Ringer's solution with alkali. Hill,⁸⁾ experimenting on humans running at various speeds, determined the lactic acid in muscles by the calculation method mentioned above, which ranged from 0.23 to 0.62% and diminished to 0.15–0.41% if a part of the acid streaming into blood or lymph is reduced from the values.

Since the exercise given by us is very mild in contrast to the running conducted by Hill,⁸⁾ the lactic acid content accumulated in muscles after the exercise is small in the patients recovered from beri-beri, but it is clearly increased in its acme.

B. Oxygen Requirement.

The definition of oxygen requirement demanded by exercise is: the total sum of the oxygen consump-

tion augmented above the resting value during exercise and its recovery, as above illustrated.

The oxygen requirement in the recovered beri-beri patients is between 2400 and 4562 c.c. with an average of 3609 c.c., while in the acme it increases to the average value of 7139 c.c., with variation between 4413 and 9228 c.c. notwithstanding the fact that in both the stages the exercise taken was of the same grade :—namely the oxygen requirement in the acme of beri-beri is 95% above that in its recovery (Table I & Fig. 1).

Eppinger,¹⁰⁾ on establishing the fact that the oxygen requirement is augmented in Grave's disease and uncompensated heart failure, supposed that this phenomenon was to attribute to some confusion in the ratio between the lactic acid to be oxidized and that to be synthesized out of the lactic acid formed due to the exercise, so that the ratio 1 : 4 being confused, the former should be increased. Even in mild cases of beri-beri where decrease in CO₂ content in venous blood is not notable, not to mention serious cases, we observed remarkable acidosis to take place as a result of muscular exercise, lasting for a long time, and we attributed this appearance to the existence of acidosis in blood, tissues, and muscles, and to a disturbance in lactic acid resynthesis. We therefore concluded that the neutralizing process against the lactic acid during its formation is not perfect, as already stated in our first report. Furthermore, we mentioned that the disorder in lactic acid resynthesis can be induced, provided that the acid-neutralizing power is thus not complete, and that in turn the acidosis and the disturbed resynthesis of lactic acid is in the relation of *circulus vitiosus*. Accordingly, it is suggested that in the acme of beri-beri the ratio of the lactic acid to be oxidized to that to be resynthesized is increased, as proved in Grave's disease and uncompensated heart failure. Then, it is right that although the lactic acid is produced in the same amount by the muscular exercise of the same extent, in the acme of beri-beri the oxygen requirement increases, for part of the lactic acid to be oxidized is increased. But to decide this problem, we must conduct another investigation.

On the other hand, beri-beri patients generally show accompanying nervous symptoms :—namely some hypaesthesia and motor disturbance of the legs. It is apparent that the motor paralysis is due also to a disorder in the nerves attached to the muscle, although a functional disorder in the muscles themselves, and their anatomical and chemical alteration are also responsible for it. It cannot be denied that the muscular exercise was carried out uneconomically, because the patients examined by us also had considerable motor disturbance in the legs, with marked circulatory symp-

toms, so that legs with incomplete innervation must expend an excessive amount of energy as they strive more than necessarily. This fact also is thought to be a cause of large oxygen requirement.

TABLE
Effect of muscular exercise on respiratory volume

No.	Subject	RV (litre) & RQ	In acme									
			Before exercise	During exercise (mins. after commencement of exercise)		After exercise (mins. after cessation of exercise)						
						2½	5	10	15	20	30	40
1	S. K.	RV RQ	5.67 0.82	15.63 0.87	19.84 0.83	10.42 0.93	9.15 1.00	8.35 1.03	6.96 1.09	6.52 0.96	5.96 0.75	6.02 0.74
2	T. N.	RV RQ	7.15 0.77	14.40 1.01	29.04 1.03	14.29 1.20	10.98 1.10	10.58 0.85	9.59 0.76	9.02 0.72	8.92 0.73	8.52 0.75
3	S. S.	RV RQ	6.22 0.90	21.31 1.12	23.46 0.89	17.97 1.50	17.56 1.70	17.39 1.10	12.61 0.93	9.35 0.80	5.94 0.83	5.72 0.88
4	T. N.	RV RQ	4.68 0.80	14.95 0.90	17.27 0.87	13.69 1.00	8.82 1.40	6.70 0.95	6.30 0.85	5.91 0.81	5.92 0.76	6.29 0.81
5	M. K.	RV RQ	5.68 0.99	17.52 1.12	25.21 0.94	15.33 1.26	11.39 1.46	9.20 1.23	7.66 1.31	7.76 1.00	6.05 0.62	6.80 0.67
6	K. S.	RV RQ	7.36 0.85	18.45 0.87	26.03 1.06	22.88 1.00	15.12 1.53	10.27 1.05	7.11 0.93	7.39 0.78	7.04 0.82	7.06 0.76
7	M. G.	RV RQ	6.38 0.95	18.03 0.82	22.08 1.10	17.20 1.29	12.13 1.30	11.40 1.26	7.86 0.90	7.95 0.91	6.97 0.84	7.40 0.85
8	T. S.	RV RQ	5.59 0.79	20.69 0.80	16.13 0.91	17.00 1.14	10.50 1.21	7.47 0.81	6.97 0.80	6.90 0.74	6.56 0.75	6.10 0.77
9	H. S.	RV RQ										
Average		RV RQ	6.09 0.86	17.62 0.94	22.38 0.95	16.10 1.17	11.96 1.34	9.67 1.04	8.13 0.95	7.60 0.84	6.67 0.76	6.74 0.78

C. Change in RQ through Muscular Exercise.

Since CO₂ increases as much as the oxygen is spent through burning of lactic acid, RQ gradually approaches 1.0 as the grade of exercise be-

III.

(RV) and RQ in beri-beri and after its recovery.

			After recovery										
			Before exercise	During ex- ercise (mins. after com- mencement of exercise)		After exercise (mins. after cessation of exercise)							
50	70	90		2½	5	2½	5	10	15	20	30	40	50
6.59 0.73	6.42 0.77	6.34 0.78	5.32 0.78	14.58 0.84	17.02 0.99	6.86 0.84	3.98 0.96	4.59 0.94	4.47 0.89	4.87 0.91	4.81 0.86	5.19 0.90	5.18 0.83
7.88 0.74	7.86 0.73	7.40 0.77	7.08 0.99	18.60 1.04	22.53 1.22	14.03 1.16	10.26 1.01	8.54 1.00	7.05 1.04	7.23 0.96	6.89 1.00	6.98 0.88	7.12 0.88
6.05 0.57	6.12 0.60	6.35 0.82	6.18 0.95	19.05 0.90	18.31 1.19	10.57 1.03	11.36 0.96	6.60 0.86	7.37 0.90	6.29 0.89	6.07 0.97	6.12 0.74	5.99 0.88
5.75 0.78	5.71 0.74	5.94 0.77	5.57 1.00	14.27 0.92	16.25 1.36	10.90 1.28	7.27 1.32	5.96 1.10	6.51 1.12	6.00 0.95	5.57 1.01	5.47 0.93	5.68 0.97
5.99 0.66	6.20 0.68	5.88 0.72	4.27 0.94	21.05 1.12	19.63 1.20	11.24 1.18	6.40 1.10	3.79 1.01	4.30 0.97	4.46 0.92	3.31 0.94	3.81 0.95	3.92 0.97
9.17 0.75	7.24 0.82	9.86 0.84	5.68 0.88	14.86 1.01	20.72 1.04	17.12 1.22	7.44 0.96	6.16 0.95	6.09 0.97	5.39 0.99	5.55 0.97	5.59 0.95	5.71 0.94
7.18 0.86	7.07 0.80	7.05 0.82											
6.39 0.77	6.79 0.70	6.56 0.72											
			5.98 0.77	15.20 0.90	19.34 0.82	16.32 0.82	8.54 0.76	7.26 0.73	6.38 0.71	5.88 0.72	5.76 0.76	5.90 0.77	5.84 0.78
6.88 0.73	6.68 0.73	6.92 0.78	5.73 0.90	16.80 0.97	19.11 1.12	12.43 1.08	7.89 1.01	6.13 0.94	6.02 0.94	5.73 0.91	5.42 0.93	5.58 0.87	5.63 0.89

comes vigorous, the burning in lactic acid occurring violently, but RQ does not exceed 1.0 by the increased burning of lactic acid alone. Hill¹¹⁾ reported, however, that it can ascend to 2.0 or more due to the discharge of CO₂ in blood and tissues through non-neutralized lactic acid.

In patients recovered from beri-beri RQ reached about 1.0 during the first half of exercise and finally exceeded 1.0 for the most part, for the exercise imposed on the examinees was slight, as above explained. In the acme of beri-beri, where the RQ at rest is generally lower than that in the convalescent state, as Okada¹²⁾ demonstrated, the change of RQ through

exercise diverges from that in recovered beri-beri patients, that is, it generally shows figures below 0.9 during the first half of exercise and on the contrary often tends to descend lower, or in rare cases surpasses 1.0 with difficulty, during the latter half (Table III & Fig. 2). In patients recovered from beri-beri RQ after the cessation of exercise sometimes becomes larger than 1.0, but smaller than the value during the latter half of exercise, and moreover it remains above 1.0 for 15 minutes after the cessation of exercise, while in the acme of beri-beri RQ, with relatively slight ascension during muscular exercise is considerably elevated immediately after the cessation of exercise, reaching the maximum value usually 5 minutes later, which is apparently greater than that in the recovered beriberi patients.

It is an interesting phenomenon that in the most serious stage of beri-beri, RQ which ascended during the first half of exercise, mostly descended during the latter half of exercise, contrary to the case in the recovered stage of beri-beri. This process seems to be related also to increased acidosis

Fig. 2.

Case 5. Effect of muscular exercise upon RQ in the acme of beri-beri (thick line) and its recovery (thin line).

11) Hill and Furusawa, Proc. Roy. Soc. London, 1924, 98, 98.

12) Okada, Iji-Koron, 1927, No. 777, 14 (Jap.).

which results from non-neutralized lactic acid accumulated in muscles. That is to say, acidosis of a certain degree dilates blood vessels, but that exceeding this limit usually contracts them, and in turn in beri-beri patients the muscles acting most violently like gastrocnemius muscles undergo a considerable acidosis, whereby blood flow in loco diminishes and becomes an importance cause of swelling in gastrocnemius muscle, as stated in our first report.¹⁾ For this reason it is quite natural that RQ is depressed, because the output of CO₂ diminishes proportionally as the non-neutralized lactic acid pouring into blood decreases as the consequence of the reduced blood flow which in turn is due to the aggravated acidity originated by the nonneutralized lactic acid amassed in muscles.

Then after exercise RQ appears to ascend due to the discharge of CO₂ through a copious flow of nonneutralized lactic acid into blood, when the blood flow increases gradually as the acidosis becomes less owing to the cessation of lactic acid production after the muscular exercise. In severe cases of beri-beri this process seems to become remarkable at 5 minutes after the cessation of exercise (Table III & Figure 2). This fact is in accord with the evidence that on determining lactic acid in cubital venous blood in the acme of beri-beri, the lactic acid content 10 minutes after the exercise is greater than that immediately after the exercise, as will be discussed in the fifth report.

In brief, we have again made this supplementary discussion regarding RQ, because the observation of RQ communicated in the first report¹⁾ was intermittently performed before and immediately after the exercise and 30 minutes later, and we had overlooked the interesting results obtained here from a continuous observation of RQ during and after the exercise, as mentioned above.

Evidence that in beri-beri patients, RQ once raised by muscular exercise diminishes about 20 minutes after the exercise, and moreover does not easily return to its resting value, is analogous to what was stated in the first report.¹⁾

D. Respiratory Volume.

In the acme of beri-beri the respiratory volume at rest and even during muscular exercise is clearly larger than that in its recovery, and the restoration in the augmented respiratory volume due to exercise also is retarded; judging from the average value, in recovered beri-beri patients the augmentation of the respiratory volume due to muscular exercise over the

resting value returns to below 10% within 10 minutes, while in severe cases it decreases below 10% by barely 70 minutes after the exercise (Table III).

E. CO₂ Output.

That in the majority of beri-beri patients the output of CO₂ is more

TABLE
Effect of muscular exercise on CO₂ output

No.	Subject		In acme									
			Before exercise	During ex- ercise (mins. after com- mencement of exercise)		After exercise (mins. after cessation of exercise)						
						0-2½	2½-5	5-10	10-15	15-20	20-30	30-40
1	S. K.	CO ₂ (c.c.) Do. %	228 4.02	696 4.45	840 4.21	384 3.69	341 3.73	369 3.84	327 4.69	224 3.42	218 3.54	206 3.41
2	T. N.	CO ₂ (c.c.) Do. %	251 3.50	952 4.69	1049 3.61	463 3.25	316 2.88	318 3.01	252 2.62	224 2.89	218 2.86	205 2.83
3	S. S.	CO ₂ (c.c.) Do. %	201 3.43	703 4.36	766 3.26	820 3.00	606 2.72	289 2.17	289 2.31	206 2.20	216 2.03	209 2.66
4	T. N.	CO ₂ (c.c.) Do. %	204 4.28	734 4.91	829 4.81	583 4.26	321 3.64	233 3.47	218 3.36	204 3.45	203 3.43	214 3.41
5	M. K.	CO ₂ (c.c.) Do. %	211 3.73	702 3.74	907 3.61	584 3.81	381 3.35	350 3.81	293 3.82	216 2.79	194 3.20	147 3.19
6	K. S.	CO ₂ (c.c.) Do. %	238 3.23	715 3.89	1023 3.92	913 3.99	517 3.25	490 4.76	328 3.12	323 3.01	216 3.03	257 2.96
7	M. G.	CO ₂ (c.c.) Do. %	205 3.17	734 4.38	1054 4.32	636 3.71	349 3.10	341 2.81	204 2.51	205 2.58	211 2.64	194 2.46
8	T. S.	CO ₂ (c.c.) Do. %	194 3.14	776 4.27	764 3.90	508 3.00	347 3.03	215 2.85	209 3.00	193 2.80	183 27.9	191 3.03
Average		CO ₂ (c.c.) Do. %	216.5 3.56	751.5 4.34	904.0 3.96	611.4 3.59	397.3 3.21	325.6 3.34	265.0 3.18	224.4 2.89	207.4 2.94	202.9 2.99

decreased in the acme than in the recovery is consisted with the evidence that in the former, RQ during muscular exercise does not increase sufficiently. And then in the acme of beri-beri the CO₂ output augmented during muscular exercise resumes its value at rest apparently late. In reviewing the average value in CO₂ output, in the acme of beri-beri it returns within the difference of 10% above the resting value in 30 minutes, but in

IV.

in beri-beri and after its recovery.

			After recovery										
			Before exercise	During ex- ercise (mins. after com- mencement of exercise)	After exercise (mins. after cessation of exercise)								
40-50	50-70	70-90				0-2½	2½-5	5-10	10-15	15-20	20-30	30-40	40-50
212 3.50	210 3.50	232 5.52	190 3.38	732 5.01	876 5.05	339 4.93	163 4.10	191 4.17	190 4.25	196 4.02	191 3.97	192 3.66	175 3.37
215 2.90	220 3.22	218 3.05	248 3.23	1091 5.04	1141 4.61	385 4.01	312 3.53	265 3.78	262 3.37	258 3.18	262 3.21	303 3.23	299 3.40
134 2.21	155 2.76	175 3.01	211 3.64	904 4.67	1028 4.40	622 3.52	223 3.15	133 2.02	150 2.82	194 3.09	214 3.27	186 2.56	194 2.98
200 3.43	193 3.38	208 3.50	185 3.32	616 4.32	658 4.05	443 4.06	290 3.99	185 3.11	201 3.86	226 3.72	210 3.65	193 3.54	188 3.28
185 3.09	180 3.12	182 3.05	160 3.74	896 4.25	911 4.64	468 4.16	235 3.67	138 3.63	134 3.57	169 3.79	148 3.20	167 3.86	152 3.92
229 2.50	239 3.05	258 3.12	195 3.43	658 4.43	936 4.53	733 3.79	258 3.29	207 3.35	203 3.35	165 3.34	161 3.07	165 2.91	182 3.26
178 2.48	117 2.24	119 2.86											
196 2.79	162 2.39	168 2.41											
193.6 2.86	184.5 2.96	195.0 3.32	194.5 3.46	816.2 4.62	925.0 4.55	498.3 4.08	246.8 3.62	186.5 3.34	190.0 3.54	201.3 3.52	197.7 3.40	201.0 3.29	198.3 3.37

Fig. 3.

Case 5. Effect of muscular exercise upon CO₂ output and CO₂ content in Expirium in the acme of beri-beri (dotted line) and its recovery (substantial line).

its recovery within only 10 minutes (Table IV & Fig. 3). In sufferers from beri-beri the CO₂ content in expirium is mostly increased during a quiet condition, but this content during muscular exercise is obviously less augmented than in the recovered beri-beri patients. It is observed that in the acme of beri-beri the average value of the CO₂ content descends below that at rest 5 minutes after muscular exercise, reaches the minimum value 50 minutes later, and is not resumed even 90 minutes afterwards; while in recovered beri-beri patients it approaches near the resting value 10 minutes after the exercise, descending no more or only slightly (Table IV & Fig. 3).

According to Haldane and Priestly¹³⁾ and Herxheimer and Kost,¹⁴⁾ respiratory volume does not run parallel to oxygen consumption, but rather varies proportionately to the CO₂ output when the gaseous exchange is altered in the case of rice-bran administration, or by muscular exercise, etc. This is supposed to depend upon the stimulation of the respiratory centre through CO₂. But Hasselbalch¹⁵⁾ stated that H-ion concentration sensitively affects the respiratory centre, and that CO₂ influences it only so far as the CO₂ output is related to H-ion concentration.

13) Haldane and Priestly, Journ. Physiol., 1905, **32**, 225.

14) Herxheimer and Kost, Zeitschr. f. klin. Med., 1928, **108**, 240.

15) Hasselbalch, Biochem. Zeitschr., 1912, **40**, 403.

Later on, this fact was confirmed by many authors' experiments on alkalosis and acidosis.

If we suppose that CO_2 alone stimulates the respiratory centre, the augmented respiratory volume in beri-beri must mean an increase in the CO_2 output ; while actually, on the contrary, the respiratory augmentation is accompanied by a decrease in the CO_2 output ; i. e., this phenomenon is caused by stimulation of the respiratory centre through increased H-ion concentration provoked by lactic acid accumulation. Furthermore, the fact that in beri-beri patients the CO_2 content in expirium is lowered, demands great ventilation in order to exhale even a small amount of CO_2 . This also shows the existence of something besides CO_2 which stimulates the respiratory centre.

That in beri-beri patients, the increase in their respiratory volume after exercise is not easily recovered is partly due to retardation in the restoration of the augmented CO_2 output, one cause of the retardation being the excessive CO_2 output corresponding to the oxygen spent for burning of lactic acid ; and the other cause, perhaps, being the discharge of CO_2 through the pouring of non-neutralized lactic acid from muscles into blood in the early stage of recovery after the exercise, especially when RQ amounts to more than 1.0. But we notice that in the sufferers from beri-beri the respiratory volume in the stage of CO_2 retention is larger than that at rest, although the CO_2 output comes to be diminished below the value at rest. It is presumed to be due to stimulation of the respiratory centre through acidosis which is not easily resumed after the exercise. Furthermore, it has been here verified, on observing the respiratory volume, that in beri-beri patients acidosis increased by muscular exercise does not easily return to the resting value, as already often demonstrated.

The fact that in cases of beri-beri the CO_2 content in exhaled air is lessened, means that the respiratory volume is increased in comparison with the CO_2 output and proves similarly that something provoking acidosis, in addition to CO_2 , stimulates the respiratory centre.

IV. DISCUSSION AND SUMMARY.

In our first report, after confirming that in beri-beri patients the lactic acid metabolism is disturbed during muscular activity, we concluded that there is an alteration of the oxygen debt and its requirement. That is to say, in these experiments we have verified the fact that the oxygen debt in beri-beri patients is augmented, and from this determined that lactic acid

easily accumulates in muscles, and recognized the oxygen requirement to increase in them. Provided that the lactic acid content to be oxidized during the resynthesis is augmented, the above phenomena can also be attributed to this cause. But as in beri-beri patients there are functional disturbances of leg nerves and muscles, it is probable that the muscles act uneconomically. Such a fact seems to be an important cause of the augmented oxygen requirement. Now we infer from the insufficient rise of RQ during muscular exercise and its surprising elevation after the exercise that in muscles acting vigorously, like the gastrocnemius muscles, acidosis in loco increases highly under muscular activity and the peripheral blood vessels in the muscles contract, whereby the blood flow may become unsatisfactory. We also infer that the surprising elevation of RQ occurs on account of the pouring of non-neutralized lactic acid into the blood as the blood flow in muscles is resumed after the suspension of muscle work. Thus, by observing the influence of muscular work on RQ and respiratory volume in beri-beri patients, we have elucidated the hard recovery in the acidosis increased by muscle work.

Acidosis and the synthetical disorder of lactic acid in beri-beri patients, appearing also in cases of experimental B-avitaminosis, may be based on a lack of vitamine-B, but both the conditions, being related to each other in *circulus vitiosus*, seem to urge reciprocal deterioration. Although it is suspected that the disturbance in lactic acid resynthesis is brought on in beri-beri patients in consequence of circulatory failure developed by them, such a supposition can be swept away when we consider that the blood flow in these patients is greater than that in healthy individuals, even during muscular exercise, not to say at rest, as stated in the second report.

In the first and second report we presumed that in beri-beri the adrenaline output is apparently also accelerated during relatively mild exercise, because the circulatory symptoms in beri-beri patients, i. e. palpitation of the heart, accentuated cardiac sounds, and descent of the minimum blood pressure, are the same as in the case where adrenaline is injected into normal subjects; and these symptoms become remarkable as a result of muscular exercise. Furthermore, in stating the adrenaline secretion to be accelerated even at rest in cases of beri-beri, we explained that the maximum blood pressure does not always necessarily ascend, for as acidosis is present, an abnormal reaction to adrenaline takes place, although its output into blood is increased. It has been demonstrated, to verify the supposition mentioned above, that there are hypertrophy and an increased amount of adrenaline present in the medullary substance of the adrenal

gland in the cadaver of beri-beri.

That the secretion of adrenaline is increased by muscular exercise seems to be physiologically congruous, if we consider that adrenaline accelerates the cardiac function, increases the circulation and effects a dilation upon the peripheral blood vessels when H-ion concentration reaches a certain limit, although it constricts the peripheral blood vessels generally, in turn hastening especially the circulation in acting muscles and other tissues where H-ion concentration is augmented. Thus, adrenaline brings on hyperglycaemia through glycogenolysis.

There are not a few authors who think that adrenaline has an action which relieves the fatigue of muscles in addition to the action mentioned above (Cannon and Nice,¹⁶⁾ Carnot und Tosserand,¹⁷⁾ Hoskins and Durrant¹⁸⁾ and Gruber¹⁹⁾). Asher²⁰⁾ found a serious condition of fatigue to arise in epinephrectomised rats when they were injected intraabdominally with the compressed fluid obtained from the exercised muscles of other epinephrectomised rats. Hauptfield,²¹⁾ on reviewing the subject, decided that the extract of the cortical substance in adrenal gland has no ability to relieve the fatigued condition mentioned above, and that the extract from the cortical substance does not neutralize the poison produced during the fatigue. Ferreira²²⁾ found on injecting the extract from the adrenal gland into frog, sheep and guinea-pig that the duration of fatigue is shortened, and in determining that the effect of the adrenal gland was related to the marrow substance of the gland or to adrenaline contained in it, obtained the same result by injecting $\frac{1}{100.000} - \frac{1}{200.000}$ adrenaline instead of the extract from the adrenal gland.

Since adrenaline is said to hasten the recovery from fatigue in this manner, it is a very rational phenomenon that we see hypertrophy in the adrenal gland when in beri-beri patients the restoration of fatigue is retarded on account of the disturbance occurring in lactic acid resynthesis due to muscular exercise. The descended minimum blood pressure, accentuated cardiac sounds, and audible arterial sounds among the circulatory syndroms, which can be provoked by adrenaline application, appear most markedly in

16) Cannon and Nice, *Americ. Journ. Physiol.*, 1913, **32**, 44.

17) Carnot and Tosserand, *Cpt. rend. d. Soc. d. Biol.*, 1902, **54**, 1472.

18) Hoskins and Durrant, *Ibid.*, 1923, **66**, 176.

19) Gruber, *Journ. Pharmac. Exp. Therapeut.*, 1924, **23**, 335.

20) Asher, *Zeitschr. f. Biol.*, 1923, **78**, 315.

21) Hauptfield, *Cpt. rend. de la Soc. de Biol.*, 1924, **90**, 1083.

22) Ferreira, *Ibid.*, 1926, **95**, 1284.

patients of beri-beri who are every day engaged in sufficient muscular work, while in patients performing no, or only mild, muscular work after suffering from beri-beri, for instance, pregnant women and youths disliking exercise, we have no experience of hearing femoral sounds or seeing a marked descent in the minimum blood pressure, notwithstanding that the appetite is lacking, the pulse rate accelerated, and the motor paralysis of limbs too considerable to allow standing. Some of the human experimental B-avitaminosis cases have symptoms identical to those in beri-beri patients who engage only in mild muscle work.

It is almost doubtless that beri-beri occurs mainly on the basis of deficiency in vitamine-B. When we consider that also in animal B-avitaminosis acidosis and various phases of resynthetical disturbance in lactic acid have been proved, in the sufferers from beri-beri the resynthetical disturbance in lactic acid during muscular work, i. e. a disturbance in recovery from fatigue, may be based on a shortage of vitamine-B and in order to remove the fatigue thus retarded in its recovery, the organism appears to accelerate the secretion of adrenaline. When the augmentation in the adrenaline output is often repeated, it is easily presumable that the adrenal gland becomes compensatively hypertrophic.

Since in beri-beri patients with serious circulatory symptoms we note acidosis and augmented lactic acid in the blood even in a quiet condition, as is seen after the vigorous muscular exercise which healthy subjects perform, it is not improbable that the muscular exercise accelerates the secretion of adrenaline, which acts relieving the fatigue, and thus increases the adrenaline content in the blood. For this reason, there are hypertrophy of the adrenal gland and an increased output of adrenaline in the cardiac form of beri-beri, a phenomenon protecting the organism, which occurs in order to oppose the lactic acid accumulation or to hasten the retarded recovery from fatigue. Hence, this phenomenon appears in the patients who have done muscular work after suffering from beri-beri, and is not perceptible in those who have not engaged in muscular exercise.

In short, in beri-beri cases occurring through deficiency in vitamine-B as a main cause of the disease, their circulatory symptoms are varied according to the degree of the muscular exercise, whereby an important cause is brought forward for the various forms of beri-beri.

V. CONCLUSION.

1. In beri-beri patients the oxygen debt is increased. This means that lactic acid accumulated in muscles at the moment after the cessation of exercise is augmented, so that the recovery from the fatigue due to the exercise is prolonged.

2. The oxygen requirement is enlarged in beri-beri patients.

3. In sufferers from beri-beri the ascension of RQ during muscular exercise, especially during the latter half of it, is mild, and becomes very remarkable 5 minutes after the cessation of the exercise. This is attributable to the fact that non-neutralized lactic acid is accumulated in the muscles concerned with the contractions during the latter half of the exercise and poured into blood after the cessation of the exercise.

4. In cases of beri-beri the respiratory volume is considerably augmented under muscular exercise, and the augmentation with difficulty returns after the exercise to the value at rest.

5. In beri-beri the CO_2 output during exercise is less increased than in health and this increase does not easily return to the resting value after the cessation of the exercise. These changes in respiratory volume and CO_2 output are due to acidosis provoked by disturbance of lactic acid metabolism above mentioned.