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Myothermic Studies On the Muscle Poisoned with Monoiodoacetic Acid.

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Abstract

1. The magnitude of the initial heat production in relation to the maximum tension developed and its time-distribution is entirely unaffected through poisoning with monoiodoacetic acid. 2. The ratio of the area of tension-time curve to the maximum tension developed, i. e. the equivalent duration of single twitch, is not affected through poisoning with monoiodoacetic acid. 3. A considerable amount of the recovery heat production takes place in the poisoned muscle under aerobic conditions, though it is less in degree than that of the normal one, and sometimes it fails entirely, as in the normal muscle under anaerobic conditions. 4. The delayed anaerobic heat production of the poisoned muscle occurs in the same degree as in that of a normal muscle. 5. From the results obtained in this investigation, some considerations were made with referrence to the chemical processes played in muscular contraction. Finally, our sincere thanks are due to Prof. Oinuma for his suggestions and advice during our experiments.

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Myothermic Studies On the Muscle Poisoned with Monoiodoacetic Acid.

By

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Introduction.

It was demonstrated by the researches of *Lundsgaard* (1930), that muscles poisoned with monoiodoacetic acid can perform a considerable amount of work without lactic acid formation. *Hill-Meyerhof*'s theory (*Hill*, 1924, 1931; *Meyerhof*, 1930) that the energy needed for the mechanical work of a muscle depends on the chemical energy resulting from the breakdown of glycogen to lactic acid, is claimed to be greatly modified by these new facts. So in the cycle of the chemical changes of muscular contraction, creatinephosphoric acid comes to play an important rôle at least in the earlier phase of muscular activity, in place of glycogen breakdown to lactic acid. According to the works of *Lundsgaard* (1930) and subsequent investigators (*Lehnartz*, 1931; *Meyerhof* and *Boyland*, 1931; *Hill*, 1932; *Eggleton*, 1929), it has been made clear that the breakdown of phosphagen is the source directly supplying energy for both aerobic and anaerobic muscular contractions, and that the breakdown of glycogen to lactic acid in the normal muscle only provides the energy for the resynthesis of creatinephosphoric acid. It is considered, therefore, in the case of the iodoacetate muscle, where the formation of lactic acid does not take place, that there is no available source of energy in the anaerobic state for the resynthesis of broken down creatinephosphoric acid.

The facts above referred to, lead us naturally to suppose that, from the point of view of the thermodynamics of muscular contraction, the initial and recovery heat productions of normal muscles, where two different decomposing and restorative processes take

place, greatly differ from those of the iodoacetate muscle, where, in the main, only one reversible chemical process (breakdown and resynthesis of creatinephosphoric acid) occurs.

The review of recent works concerning this question indicate that:

1) The ratio Tl/H in a muscle twitch or in tetanic contraction is the same in the poisoned muscle as in a normal muscle (*Fischer*, 1931; *Hill* and others, 1931; *Meyerhof* and others, 1930).

2) The amount and distribution of the initial heat is not affected by preventing lactic acid formation (*Fischer*, 1931; *Hartree*, 1931).

3) Moderate prolongation of the relaxation heat appears and this is more marked than the lengthening of the relaxation of muscular contraction (*Fischer*, 1931).

4) There is no delayed heat production (nachträgliche Wärme, aber nicht Erholungswärme nach *Fischer*) in the poisoned muscle, but it does appear in the normal one.

5) The recovery heat production of a normal muscle does not take place in the poisoned muscle (*Fischer*, 1931), while according to *Hill* and others (1931) there is recovery heat production in the same amount as in the normal muscle and its time distribution shows much prolongation.

6) From the studies of the change of osmotic pressure and the total heat produced in exhaustion of the iodoacetate muscle, granted certain assumptions, it is accepted that the same energy liberating chemical change in the poisoned muscle is also found in the normal one, together with lactic acid formation and its restoration (*Hill* and *Parkinson*, 1931).

Our present investigation has been directed to the aerobic and anaerobic heat productions of iodoacetate muscle with special reference to its relation to the normal, in view of the results obtained by *Lundsgaard* and others.

Experimental

A.) Apparatus.

1) Thermopile.

A new type of thermopile recently improved by *Hill* (1928) was used throughout the experiments. The thickness of the insulation of bakelite and shellac was reduced as far as possible in order to avoid delay in the conduction of heat produced by muscular contraction. To ensure complete insulation, following the *Hill*'s instruction, the thermopile was dipped every time before use in molten paraffin, mixed with white beeswax (melting point 42°C). Silver electrodes were cleaned, the lower

of which was fixed between the sartorius muscles at their attachment to the pelvic bone attached by a muscle clump, the upper one surrounded the distal end of the muscles, extended by fine inextensible enamel wire passing through a metal tube to an isometric lever. The glass chamber, about 150 cc, volume was filled with *Ringer*'s fluid in which the thermopile was dipped, and provided with gas exit and inlet pipes.

2) Galvanometer.

The galvanometer used was the Kelvin type of astatic moving magnet made by *Downing* as it is superior to the moving coil type in its sensitivity and rapidity of response. To protect it from outer mechanical and electrical disturbances, the galvanometer was placed on a suspension and shielded with an iron cover. Galvanometer zero was adjusted easily by the small adjusting magnet placed on the wooden frame before the galvanometer. This instrument gives a deflection of about 100 mm for a 0.1 sec. tetanus on the scale at 2 meters distance.

3) Recording System.

In order to determine the time-relations of the initial heat produced in 0.1 sec. tetanus of sartorius muscle, photographic recordings were taken, employing Ilford special rapid plate of 16 × 12 cm size, on which a beam of light from a narrow vertical slit before a pointlite lamp was recorded as a sharp black line. A *Jaquet*'s chronometer interrupting the beam of light at an interval of 0.2 sec. was placed in front of the slit. Just before the slit a magnetic shutter was also provided, the release of which coinciding with the beginning of stimulation, the beam of light was reflected from the mirror of galvanometer on to the moving plate and the deflection was recorded. Thus the earlier part of the deflection of galvanometer (5 seconds) was photographed on a plate falling at a desired speed (Cambridge plate camera with oil buffer was used).

4) Thermostat.

As the thermostat used was a large vessel filled with water and as our experiment was performed during the winter season, it was easy to ensure the constant temperature as required. The temperature of the thermostat was adjusted to the same temperature as that of the room which was previously heated to desired temperature (usually between 12° – 14°C). Thus throughout one series of experiment, even if it usually extended over a considerably long time, no change occurred in the temperature of the thermostat from the degree set at the beginning of the experiment. The constancy of galvanometer zero, therefore, was attained without any inconvenience.

5) Calibration and Analysis.

After killing the muscle with chloroform or by "electrocution" at the end of each experiment, a heating current of 20 volts a.c. for the control curve was passed through the muscle during 0.1 second. The interval for analysis was usually 0.2 second. Following *Hill* (1913) and *Doi* (1921) the method of "deflection calibration" was adopted.

Two control curves occasionally taken on the same dead muscle, did not always coincide in their deflection time curve, consequently some negative or positive remainder usually occurred in the results of analysis, contrary to the observations of Hartree. But as it does not greatly affect the results of the analysis, it may be considered practically that there is no remainder.

In the analysis of the total heat production, correction of the base-line due to

the increase of osmotic pressure and the increment of the resting heat rate were required (*Hill*, 1928).

6) Miscellaneous.

a. Gas : ... For the experiment of anaerobiosis, hydrogen gas produced by *Kipp*'s apparatus was used instead of nitrogen.

b. Muscles employed : ... Throughout our experiments, double sartorius muscle of R. nigromaculata was used.

c. Stimulation : ... Maximum stimulation derived from 4 volt a. c. of 0.1 sec. duration was applied.

d. Mechanical Response : ... The tension lever attached to the muscle through the metal tube of the thermopile chamber, gave 10 mm deflection for 17.5 grammes. The tension-time curve was recorded on kymographion revolving at high speed.

B.) Experimental Procedure.

Concentration of Monoiodoacetic Acid Solution :— As there are various opinions on the degree of concentration of monoiodoacetic acid solution most suitable to be applied to the muscle, its effect on the results (*Hill*, 1931 ; *Hartree*, 1931), it is well to state that the concentration of the drug employed in our experiments was as follows.

A stock solution of 1.0 p. c. was prepared. This was neutralised with sodium carbonate directly before used and added to *Ringer*'s fluid, the final concentration being 1/15,000. This concentration, though slightly higher than that employed by others (*Hill, Hartree*), is sufficient to poison the muscle after half an hour's soaking at room temperature.

The experimental procedure was as follows : —

1) After soaking for half an hour in *Ringer*'s fluid, air was introduced in the thermopile chamber, and stimulation was applied after waiting 30 minutes more (aerobic heat production of normal muscle).

2) Air was replaced by pure hydrogen gas, and stimulation was given after 30 minutes (anaerobic heat production of normal muscle).

3) The iodoacetate *Ringer*'s fluid was introduced and the muscle was soaked in it for 30 minutes. Then it was replaced by air and 30 minutes or more allowed to elapse. Stimulation was applied (aerobic heat production of the iodoacetate muscle).

4) Air was replaced by pure hydrogen. Stimulation was given after 30 minutes (anaerobic heat production of the poisoned muscle).

The results obtained from these experiments will be given in the next chapter.

Experimental Results.

1.) Initial heat Production and its Relation to the Tension developed.

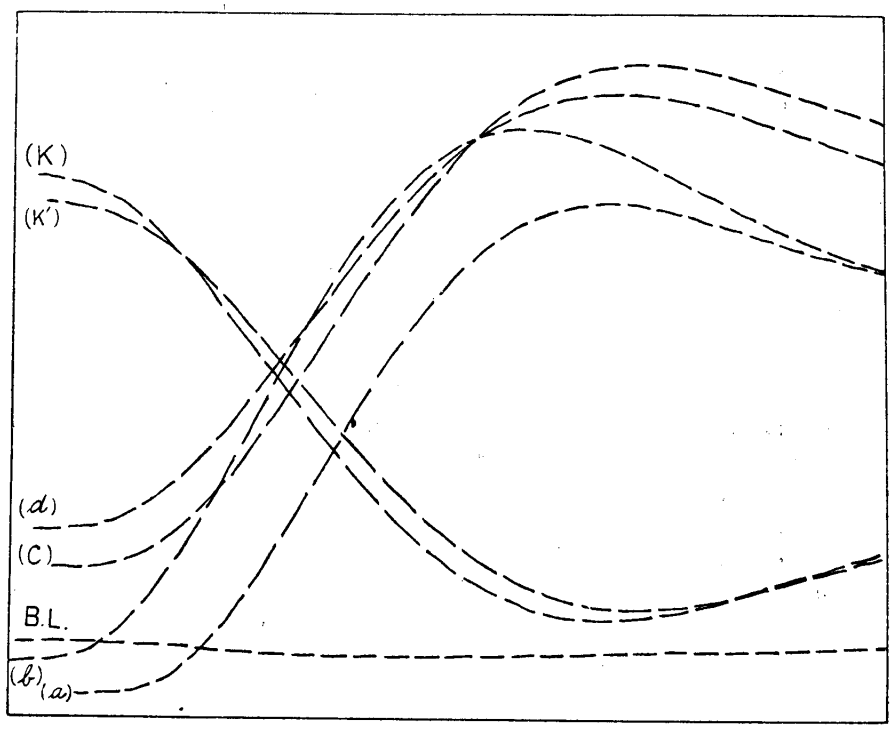
From the results obtained by the analysis of the photographic recordings of galvanometer deflection, it will be seen that the time-

distribution and the magnitude of initial heat production are usually not affected through the poisoning of monoiodoacetic acid, though in some cases the poisoned muscle with irregular heat production is observed afterwards, supposedly accompanied by the irregular form of muscular contraction.

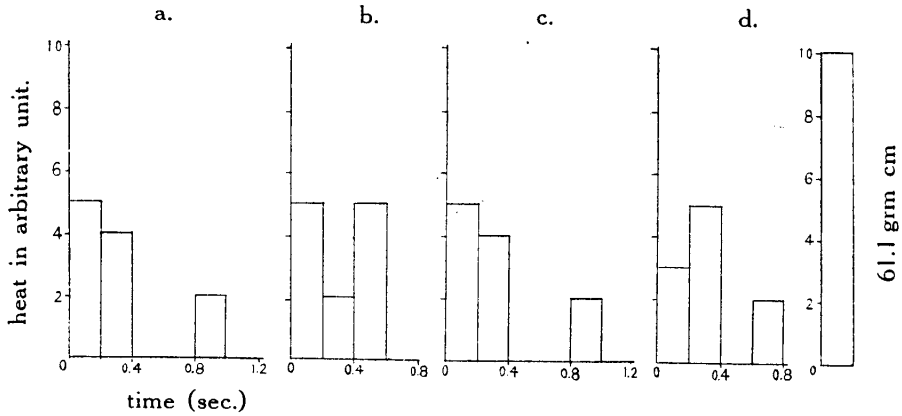
It was confirmed in the case of poisoned muscle that there were differences in the initial heat production of normal muscle in aerobic and anaerobic conditions as *Weizsäcker* (1914) at first found.

The fact, described by *Fischer* (1931), of the "spreading out" of the relaxation heat may be attributed to this irregularity of muscular contraction. Usually, however, our results on the initial heat production are similar to *Hartree*'s who reported, it is impossible to tell from the results of the analysis whether the muscle is under the effects of iodoacetic acid or not.

Fig. 1.
Analysis of the initial heat production.



(a) Normal muscle under aerobic condition.
(b) Normal muscle under anaerobic condition.
(c) Monoiodo-muscle under aerobic condition.
(d) Monoiodo-muscle under anaerobic condition.
B.L. Base-line.
K, K' Control curves.



a. Normal muscle under aerobic condition.
b. Normal muscle under anaerobic condition.
c. Monoiodo-muscle under aerobic condition.
d. Monoiodo-muscle under anaerobic condition.

Table 1.

The initial heat production and its correlating factors under aerobic condition.

Date and Temperature		Area of Tension-Time Curve (A) $(mm)^2$	Max. Tension (T) (grm)	T l (grm cm)	Initial Heat (Hi) (grm cm)	$\frac{T\,l}{Hi}$	$\frac{Hi}{T\,l}$ (micro-cal.)	Equi-valent Duration $\left(\frac{A}{T}\right)$
11/I ♂ Temp.: 13°C	$N\text{-}O_2$	66	45.8	338	61.5	5.5	4.3	1.4
	$M\text{-}O_2$	52	37.2	275	54.0	5.1	4.8	1.4
16/I ♀ Temp.: 8°C	$N\text{-}O_2$	193	54.8	356	87.1	4.2	5.8	(3.5)
	$M\text{-}O_2$	121	48.2	313	70.8	4.4	5.4	(2.5)
17/I ♀ Temp.: 14°C	$N\text{-}O_2$	118	67.0	476	71.0	6.7	3.6	1.8
	$M\text{-}O_2$	104	65.6	465	70.7	6.6	3.6	1.6
18/I ♀ Temp.: 12°C	$N\text{-}O_2$	92	42.8	304	52.7	5.8	4.1	2.1
	$M\text{-}O_2$	44	23.7	168	32.8	5.1	4.7	1.9
19/I ♂ Temp.: 13°C	$N\text{-}O_2$	103	47.5	334	63.0	5.3	4.5	2.2
	$M\text{-}O_2$	117	51.1	347	54.4	6.2	3.7	2.3
20/I ♂ Temp.: 13°C	$N\text{-}O_2$	88	46.4	304	58.6	5.2	4.5	1.9
	$M\text{-}O_2$	65	38.9	257	42.4	6.1	3.9	1.7
21/I ♀ Temp.: 13°C	$N\text{-}O_2$	97	45.4	299	64.2	4.7	5.3	2.1
	$M\text{-}O_2$	45	24.7	163	42.0	3.9	6.1	1.8
Mean value	$N\text{-}O_2$					5.3	4.6	1.9
	$M\text{-}O_2$					5.3	4.6	1.8

Note: $N\text{-}O_2$, normal muscle under aerobic condition.
$M\text{-}O_2$, monoiodoacetate muscle under aerobic condition.
l, muscle length (cm).

Table 2.
The initial heat production and to it correlating factors under aerobic and anaerobic conditions.

Date and Temperature		Area of Tension-Time Curve (A) (mm^2)	Max. Tension (T) (grm)	T l (grm cm)	Initial Heat (Hi) (grm cm)	$\frac{T\,l}{Hi}$	$\frac{Hi}{T\,l}$ (micro-cal.)	Equi-valent Duration $\left(\frac{A}{T}\right)$
26/I ♂ Temp.: 13°C	$N\text{-}O_2$	84	38.6	251	54.7	4.6	5.1	2.2
	$N\text{-}H_2$	52	28.9	188	38.3	4.9	4.8	1.8
	$M\text{-}O_2$	76	31.9	207	43.7	4.7	5.0	2.4
	$M\text{-}H_2$	47	28.3	184	32.8	5.6	4.2	1.7
28/I ♂ Temp.: 13°C	$N\text{-}O_2$	127	43.8	246	75.5	3.3	7.2	2.9
	$N\text{-}H_2$	104	46.4	260	59.3	4.4	5.4	2.3
	$M\text{-}O_2$	80	34.0	191	64.7	3.0	8.0	2.4
	$M\text{-}H_2$	58	27.3	153	43.2	3.5	6.6	2.1
30/I ♂ Temp.: 12°C	$N\text{-}O_2$	97	38.6	230	92.9	2.5	9.5	2.5
	$N\text{-}H_2$	78	36.1	215	76.5	2.8	8.3	2.2
	$M\text{-}O_2$	52	29.4	175	49.2	3.6	6.6	1.8
	$M\text{-}H_2$	43	20.6	122	43.7	2.8	8.4	2.1
31/I ♀ Temp.: 12°C	$N\text{-}O_2$	88	52.0	355	67.2	5.3	4.5	1.7
	$N\text{-}H_2$	94	53.5	365	73.4	5.0	4.7	1.8
	$M\text{-}O_2$	87	46.4	317	67.2	4.7	5.0	1.9
	$M\text{-}H_2$	78	48.5	331	61.1	5.4	4.3	1.6
1/II ♀ Temp.: 12°C	$N\text{-}O_2$	123	50.0	342	70.2	4.9	4.8	2.5
	$N\text{-}H_2$	102	53.5	366	64.4	5.7	4.2	1.9
	$M\text{-}O_2$	113	50.0	342	70.2	4.9	4.8	2.3
	$M\text{-}H_2$	133	55.7	380	76.1	5.0	4.7	2.4
2/II ♂ Temp.: 13°C	$N\text{-}O_2$	91	63.3	408	98.0	4.2	5.6	1.4
	$N\text{-}H_2$	88	62.9	405	85.5	4.7	5.0	1.4
	$M\text{-}O_2$	105	60.3	389	91.8	4.2	5.6	1.7
	$M\text{-}H_2$	95	59.2	382	85.5	4.5	5.3	1.6
3/II ♀ Temp.: 12°C	$N\text{-}O_2$	124	49.0	320	93.8	3.4	6.9	2.5
	$N\text{-}H_2$	77	43.8	286	76.1	3.8	6.3	1.8
	$M\text{-}O_2$	61	33.5	218	58.5	3.7	6.3	1.8
	$M\text{-}H_2$	61	37.1	242	70.2	3.4	6.8	1.6
Mean value	$N\text{-}O_2$					4.0	6.2	2.2
	$N\text{-}H_2$					4.6	5.5	1.9
	$M\text{-}O_2$					4.1	5.9	2.0
	$M\text{-}H_2$					4.3	5.8	1.9

Note: $N\text{-}O_2$, normal muscle under aerobic condition.
$N\text{-}H_2$, „ „ „ anaerobic condition.
$M\text{-}O_2$, monoiodoacetate muscle under aerobic condition.
$M\text{-}H_2$, „ „ „ anaerobic condition.

Also the maximum tension developed (T) multipied by the muscle length (l) in relation to the initial heat production (Tl/H) is un-

affected by the poisoning of the drug. The results are presented in Fig. 1 and Table 1 and 2.

One of the characteristics of muscular contraction, i.e. the equivalent duration of the isometric contraction [area of the tension-time curve (A)/the maximum tension developed (T)], was not altered by iodoacetate poisoning, contrary to the suggestion of previous experiments (H.K. unpublished).

A long soakting in *Ringer*'s fluid or in monoiodoacetate, had a harmful effect on the muscle, especially in the anaerobic condition. But it is not a matter of importance.

2.) The Recovery Heat Production in Aerobic Condition.

The time-relations and the magnitude of the recovery heat production under aerobic condition were obtained from analysis of the galvanometer deflection curve with the control curve of the heating current.

Two series of seven experiments on normal and poisoned muscles were performed, from which the recovery heat in normal muscle, on an average 0.55 (series A) and 0.70 (series B), in the poisoned one 0.25 (series A) and 0.35 (series B) as against of 1.1 (*Hill* and others, 1931) was obtained.

The lower value of the recovery heat of normal muscle obtained here, may be due to the fact that the recovery heat in our case was measured in the air instead of in pure oxygen (*Hill*, 1913), and that the reading of the galvanometer deflection was not recorded later than 10 minutes after the beginning of the stimulation. However, the evidence that a considerable amount of recovery heat production takes place in the poisoned muscle is a fact beyond dispute (see Fig. 2 and Table 3), although it is less than in the normal one.

But sometimes there occurs no recovery heat production, even under aerobic conditions, of the fully poisoned muscle, as *Fischer* (1931) established, and this, according to *Lundsgaard*, may be attributed to the inhibition of the respiration of the poisoned muscle through the action of the drug, an influence which differs with specimens.

Our own results did not confirm the phenomena observed by *Hill* and others (1931) the "spreading out" of the recovery heat production in the poisoned muscle.

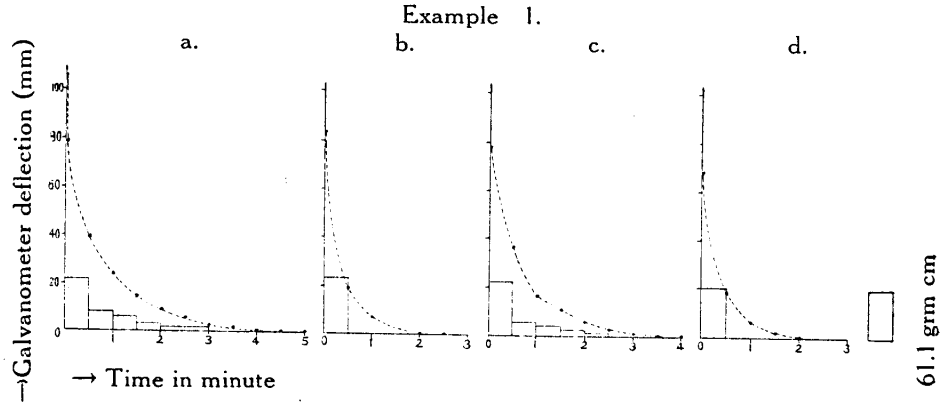
3.) Delayed Anaerobic Heat Production.

Delayed anaerobic heat production was obtained from the analysis of the area of the galvanometer deflection curve with the control

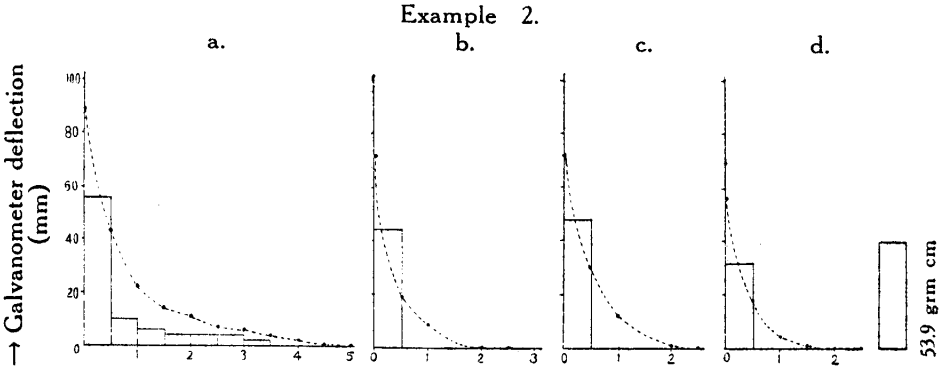
curve, after *Blaschko* (1930). Especially in this method of analysis, correction is required for the change of the base-line due to the increment of the resting heat rate after the stimulation, otherwise the results obtained show great variety from one to another.

From the results obtained it is concluded that the delayed anaerobic heat production occurs in the same degree in normal muscle as in the poisoned one, amounting to 14.6 p.c. of the initial heat production in the poisoned, 19.0 p.c. in normal muscle (mean of seven experiments).

Fig. 2.
Analysis of the recovery heat production.
Total Heat Production.

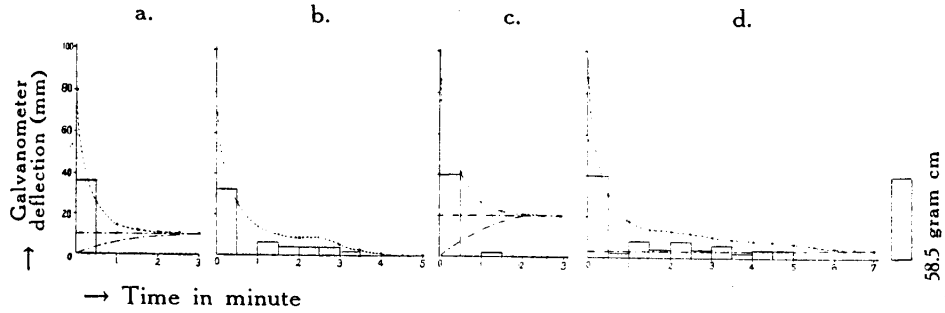


a. Normal Muscle under Aerobic Condition.
b. Normal Muscle under Anaerobic Condition.
c. Monoiodo-Muscle under Aerobic Condition.
d. Monoiodo-Muscle under Anaerobic Condition.



a. Normal Muscle under Aerobic Condition.
b. Normal Muscle under Anaerobic Condition.
c. Monoiodo-Muscle under Aerobic Condition.
d. Monoiodo-Muscle under Anaerobic Condition.

Example 3.



a. Monoiodo-Muscle under Aerobic Condition. (30 Minutes)
b. Monoiodo-Muscle under Aerobic Condition. (1 hour)
c. Monoiodo-Muscle under Aerobic Condition. (1 hour)
d. Menoiodo-Muscle under Aerobic Condition. (1.5 hours)

Table 3.
The ratio of aerobic recovery heat production (Hr) to initial heat production (Hi) : Hr/Hi.

No of Experiments. The ratio of aerobic recovery heat production (Hr) to initial heat production (Hi) Hr/Hi.

Series A.	Normal muscle	Monoidoacetate muscle
1	1.01	0.75
2	0.63	0.30
3	0.44	0.24
4	0.43	0.00
5	0.22	0.28
6	0.56	0.10
7	0.53	0.09
Mean value	0.55	0.25
Series B.		
1	0.50	0.40
2	0.47	0.58
3	0.50	0.00
4	0.96	0.50
5	1.04	0.58
6	0.37	0.39
7	1.06	0.00
Mean value	0.70	0.35

This coincides with the results recently obtained by *Hill* (1928) and *Cattell* and *Hartree* (1932).

Discussion.

The following observations are noteworthy in surveying our researches.

1) The initial heat production and some mechanical representations involved in the initial phase of muscular contraction, are not affected by the poisoning of monoiodoacetic acid.

2) In the recovery process of muscular contraction, a considerable amount of heat, though less than in normal conditions, is produced also in the poisoned muscle under aerobic conditions. But it falls under anaerobic conditions, and an increase of the resting heat rate after stimulation is observed.

3) In some experiments in the poisoned muscle, there occurred delayed anaerobic heat production in the same degree as in the normal muscle.

As there was no lactic acid formation, but uninterrupted initial heat production and mechanical performance, we cannot agree with *Hill-Meyerhof*'s theory concerning muscular activity and adopt the phosphagen hypothesis with some reservations. Initial heat production in aerobic as well as anaerobic conditions, must be due to exothermic breakdown of phosphagen.

Regarding the delayed heat production under aerobic conditions, we must assume there is resynthesis of phosphagen from the decomposed product, receiving energy liberated by oxidation of themselves (*Meyerhof, Lundsgaard* and *Blaschko*, 1930; *Fischer*, 1930; *Hill* and others, 1931; *Cattell* and *Lundsgaard*, 1933; *Ritchie*, 1933).

$$\text{Phosphagen} \underset{\text{initial heat production}}{\overset{\text{delayed aerobic heat production}}{\rightleftharpoons}} \text{creatine} + \text{phosphoric acid}$$

According to *Lundsgaard*, monoiodoacetic acid acts upon two enzyme systems, i.e. the glycogen-lactic acid system and the oxidation system, among these the former at first interrupted. Moreover there is a narrow limit of monoiodoacetic cid concentration which influences the former system and leaves intact the latter. Also he described how the poisoned muscle can perform much more work under aerobic than anaerobic conditions, and recently *Mawson* (1932, 1933) confirmed that the poisoned muscle can utilize (although it is not sufficient) the added lactate for the resynthesis of creatine and phosphoric acid. This chemical process, considered as a partial recovery process due to oxidation, necessitates heat production as a physical representation, as in our results. The failure of the aerobic

heat production sometimes observed, is attributed to the inhibition of the enzyme system of oxidation, through the action of the drug. But it is regretable, in the present state of our knowledge, that the connection between those chemical processes and physical phenomena is not yet established.

During the past 10 years there have been many studies on the delayed anaerobic heat production (*Hartree* and *Hill*, 1922, 1923; *Furusawa* and *Hartree*, 1926; *Hartree* and *Hill*, 1928; *Hartree*, 1929; *Blaschko*, 1930; *Cattell* and *Hartree*, 1932) after tetanic contraction or a single twitch, which have failed to find any physical or chemical explanation for its occurence. Among these explanations, the physical phenomena are discussed in the recent investigations on the hypothesis that a considerable fraction of the total lactic acid production occurs after the contraction is over (*Lehnartz*, 1931; *Lundsgaard*, 1931; *Meyerhof*, and *Schulz*, 1931). But considering from our results that anaerobic delayed heat production occurs also in the normal one, this heat production is not explained by delayed lactic acid formation, but is rather to be attributed, from the fact that it persists usually for a minute or two, to an unknown chemical process such as phosphagen restoration.

Summary.

1. The magnitude of the initial heat production in relation to the maximum tension developed and its time-distribution is entirely unaffected through poisoning with monoiodoacetic acid.

2. The ratio of the area of tension-time curve to the maximum tension developed, i.e. the equivalent duration of single twitch, is not affected through poisoning with monoiodoacetic acid.

3. A considerable amount of the recovery heat production takes place in the poisoned muscle under aerobic conditions, though it is less in degree than that of the normal one, and sometimes it fails entirely, as in the normal muscle under anaerobic conditions.

4. The delayed anaerobic heat production of the poisoned muscle occurs in the same degree as in that of a normal muscle.

5. From the results obtained in this investigation, some considerations were made with referrence to the chemical processes played in muscular contraction.

Finally, our sincere thanks are due to Prof. *Oinuma* for his suggestions and advice during our experiments.

References.

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