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**Physiology.** — "*On the refractory stage of the frog's gastrocnemius*".

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The values given for the length of the refractory stage — the short time following upon an ultra maximum stimulus, during which a new stimulation has no effect — are widely different.

As a rule the time of the refractory stage is considered equal to that of the latent period for which TIGERSTEDT<sup>1)</sup> by a great number of experiments found an average of 0.005". TIGERSTEDT likewise found that this value was affected by changes relating to the temperature, the kind of stimulus, its strength, the tension or to the mass to be moved. According to WALLER<sup>2)</sup> fatigue lengthens the latent period.

HELMHOLTZ<sup>3)</sup>, determining the length of the refractory stage itself arrived at  $\frac{1}{800}$ " (that is about 0.0016"), KRONECKER and STANLEY HALL<sup>4)</sup> at  $\frac{1}{143}$ " (about 0.007") and sometimes  $\frac{1}{300}$ " (about 0.0032"), and SAMJLOFF<sup>5)</sup> at 0.002".

As regards the effect of various circumstances on the length of the refractory stage I could find no data. SCHENCK<sup>6)</sup> saw that fatigue and ISHIHARA<sup>7)</sup> that refrigeration were unfavourable to the summation, which is of course stronger in proportion as the second stimulus reaches the muscle at a moment when it is able to show distinctly that it is stimulated.

To determine whether the length of the refractory stage is influenced by various circumstances and if so, in what direction and to what extent, the following experiments were made.

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1) Archiv. f. Physiologie 1885 Supplement.

2) LUCIANI. Physiologie des Menschen III.

3) Verhandl. der Kön. Preuss. Akademie 1854.

4) Archiv. f. Physiologie 1879 Supplement.

5) Pfl. Archiv. Bd. 143.

6) Pfl. Archiv. Bd. 96.

7) Pfl. Archiv. Bd. 111.

*Fatiguē.*

The gastrocnemius of a frog which had been poisoned with curarine was prepared in the usual way, and fastened to a lever with a counter-weight of 5 grammes; the whole weight acting on the muscle amounted to 10 grammes. The electrodes were fastened to the femur and to the tendon. The curves were written on the rooty paper of a fall-rotatorium as indicated by SCHENCK. For the untired muscle the minimum distance was found at which two stimuli still gave a summation of the contractions, and then after the fatigue caused by a number of induction-shocks (100 in 1'), the stimuli were applied at the same distance from each other. If the refractory stage was lengthened by fatigue of the muscle, which might with some ground be expected, then it would appear in a simple and conclusive way from the fact that a stimulus-interval only just causing summation before the fatigue, would give no summation if the muscle was fatigued, whilst by lengthening the interval so much that summation only just set in, the new length of the refractory stage might be arrived at. I succeeded, however, but seldom in finding quickly the stimulus-interval which differed so little from the refractory stage, that an increase of the latter must be the cause of the entire disappearance of the summation. In most cases I had to content myself with investigating the changes which underwent the degree of summation i. e. the difference between the contraction-heights caused by one and by two stimulations, expressed in the contraction-height after one stimulation.

As an example of one experiment first number 4.

At an interval of 0.002" summation sets in amounting to 0.1; after fatigue by means of 400 break shocks the summation is reduced to 0. Lengthening of the stimulation-interval to 0.005" scarcely causes the summation to return: it becomes 0.043; at a stimulation-distance of 0.015" the degree of summation has become 0.12.

In experiment 64 fatigue caused by a great many break and make shocks changes a degree of summation of 0.066 successively to 0.069, 0.08, 0.07, 0.07, 0.109, 0.14, 0.13, 0.08, and 0.09. The stimulation-interval is always 0.0053".

The following is experiment N<sup>o</sup>. 20.

After 25 break and make-shocks the degree of summation, which was at first 0.14 has become 0. Lengthening of the stimulation-interval from 0.0025" to 0.004" raises it again to 0.04. After 125 shocks the summation has disappeared again, whilst an increase of the stimulus-interval to 0.0063" still gives a summation of 0.12.

30 experiments gave the following results.

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Number of the experiment	Temperature	Stimuli applied	Stimulation interval	Contraction height after one stimulation	Degree of summation
1	?	0	0.005"	15.3 mm.	0.11
		—	"	8.5	0.179
2	10°	0	0.0075"	20.5	0.073
		400 O.S.	"	24.5	0
3	14°	0	0.0033"	14	0.14
		300 O.S.	"	7	0.214
		450 "	"	2	0.5
4	10°	0	0.002"	20	0.1
		400 O.S.	"	22.5	0
		"	0.005"	23	0.043
		"	0.015"	25	0.12
5	11°	0	0.002"	24.5	0.06
		400 O.S.	"	22	0.02
6	13°	0	0.0034"	27	0.08
		300 O.S.	"	29	0.04
		900 "	"	19.5	0.13
		900 + 1/2 h. rest	"	21.5	0.07
		1300 O.S.	"	11.5	0.39
		1700 "	"	6	1
		0	"	25	0.16
7	13°	0	"	25	0.16
		300 O.S.	"	29	0.031
		600 "	"	22.5	0.02
		900 "	"	15.3	0.11
9	13°	0	0.004"	23	0.19
		250 O.S.	"	11	0.09
		450 "	0.008"	5	0
10	?	0	0.0068"	29	0.21
		300 O.S.	"	25	0.08
		600 "	"	10	0.2
		700 "	"	7.5	0.06
		800 "	"	4.5	0.11

Number of the experiment	Temperature	Stimuli applied	Stimulation interval	Contraction height after one stimulation	Degree of summation
11	22°	0	0.0036"	14.5 mm.	0.1
		50 O.S.	"	10.6	0.03
		125 "	"	6.75	0.03
		175 "	"	4	0.25
12	22°	0	0.005"	60	0.06
		400 O.S.	"	18	0.02
13	22°	0	0.0045"	63	0.05
		250 O.S.	"	15.5	0.18
14	21°	0	0.0054"	59.5	0.06
		25 O.S.	"	40	0.32
		65 "	"	29	0.005
		215 "	"	13	0.077
15	22°	0	0.0042"	12.6	0.19
		100 O.- and C.S.	"	8	0.125
		200 "	"	5.5	0.09
16	22°	0	0.0036"	36	0.028
		50 O.- and C.S.	"	31.5	0.03
		300 "	"	17	0.09
17	21°	0	0.0039"	46.3	0.028
		100 O.- and C.S.	"	47.5 ?	0.055 ?
		200 "	"	42	0.07
		300 "	"	35	0.09
		400 "	"	25.5	0.04
		600 "	"	7	0.28
18	21°	0	0.003"	40.5	0.11
		75 O.- and C.S.	"	40.5	0.03
		125 "	"	30	0.01
		125 "	0.005"	23	0.22
		175 "	0.003"	7	0.07

Number of the experiment	Temperature	Stimuli applied	Stimulation interval	Contraction-height after one stimulation	Degree of summation
19	22°	0	0.003"	42.5 mm.	0.07
		10 O.- and C.S.	"	41	0.1
		20 "	"	42	0.06
		30 "	"	42	0.08
		40 "	"	41.6	0.08
		80 "	"	39.5	0.05
		130 "	"	39	0.05
		130 "	"	36	0.05
		155 "	"	35.5	0.04
		175 "	"	33	0.03
		225 "	"	30.5	0.08
		225 "	"	27.5	0.07
		255 "	"	20	0.3
		255 "	"	24	0.04
20	22°	0	0.0025"	54.5	0.14
		15 O.- and C.S.	"	56.5	0.02
		30 "	"	55	0.037
		45 "	"	55.25	0.03
		75 "	"	49.5	0
		75 "	"	54 ?	0 ?
		85 "	"	54	0.04
		95 "	"	53	0
		95 "	0.004"	53	0.04
		105 "	"	51	0.06
		115 "	"	49	0.02
		125 "	"	49	0
		125 "	0.0063"	46	0.12
		225 "	"	43.5	0.1
325 "	"	35.5	0.07		

Number of the experiment	Temperature	Stimuli applied	Stimulation interval	Contraction-height after one stimulation	Degree of summation
21	22°	0	0.004"	65 mm.	0.16
		10 O.- and C.S.	"	67.5	0.07
		20 "	"	67	0.08
		40 "	"	70	0.05
		60 "	"	65	0
		60 "	0.005"	65	0.04
		80 "	"	62	-0.005
22	23°	0	0.003"	45.5	0.08
		15 O.- and C.S.	"	46	0
		15 "	0.0046"	46	0.11
		30 "	"	53	0.086
		50 "	"	42.7	0.14
		80 "	"	41.7	0.11
		130 "	"	39.5	0.11
		130 "	0.003"	41	0.01
		205 "	"	34	0
23	23°	0	0.003"	52	0.11
		20 O.- and C.S.	"	45.5	0
		20 "	0.0056"	38	0.19
		45 "	"	37	0.14
		70 "	"	34.5	0.1
		95 "	"	30	0.13
		115 "	"	28	0.14
		165 "	"	25	0.02
		205 "	"	16.5	0
24	25°	0	0.003"	49	0.08
		10 O.- and C.S.	"	49	0.06
		30 "	"	48	0.07
		50 "	"	47	0.09
		70 "	"	41	0.03
		90 "	"	22.5	0.07
		110 "	"	16.5	0.09
		130 "	"	7	0

Number of the experiment	Temperature	Stimuli applied	Stimulation-interval	Contraction-height after one stimulation	Degree of summation
25	25°	0	0.0033"	—	—
		10 O.- and C.S.	"	73 mm.	0.04
		30 "	"	69	0.05
		45 "	"	67.7	0.03
		60 "	"	69	0.0007
		75 "	"	59.5	0.03
		90 "	"	57	0.09
		120 "	"	47.5	0.17
		170 "	"	38	0.21
		220 "	"	30.5	0.25
		220 "	"	19	0
		230 "	"	11	0.18
		240 "	"	7.5	0.13
		250 "	"	3.5	0
		250 "	"	0.0066"	3.5
26	25°	0	0.0033"	—	—
		10 O.- and C.S.	"	66	0.023
		20 "	"	70	0.007
		30 "	"	69	0
		45 "	"	56.5	0.035
		60 "	"	47	0.032
		70 "	"	38	0
27	26°	0	0.0036"	58	0.10
		10 O.- and C.S.	"	56 ?	0.044 ?
		20 "	"	37	0.04
		30 "	"	26.5	0.113
		40 "	"	13	0.115
32	?	0	0.0036"	38.5	0.3
		10 O.- and C.S.	"	43	0.18
		20 "	"	43	0.16



Number of the experiment	Temperature	Stimuli applied	Stimulation-interval	Contraction-height after one stimulation	Degree of summation
32	?	40 O.- and C.S.	0.0036"	43.5 mm.	0.11
		140 "	"	41	0.09
		260 "	"	35	0.09
		340 "	"	30	0.09
		340 "	"	29.5	0.02
		385 "	"	27	0.09
		435 "	"	24.5	0.05
		465 "	"	23	0.011
64	12°	0	0.0053"	38	0.066
		250 O.- and C.S.	"	44.5	0.069
		500 "	"	43	0.08
		800 "	"	35.5	0.07
		800 "	"	28	0.07
		820 "	"	25.25	0.109
		870 "	"	25	0.13
		1020 "	"	25	0.08
65	9°	1220 "	"	22	0.09
		0	0.0053"	44	0.023
		200 O.- and C.S.	"	59	0.07
		400 "	"	50	0.09
66	11°	600 "	"	39	0.13
		0	0.0058"	44.5	0.13
		200 O.- and C.S.	"	59.5	0.075
		400 "	"	53	0.04
		600 "	"	45.5	—
		800 "	"	32	0.22

From the above values it appears, that the stimulation interval which, before fatigue sets in, only just produces distinct summation, varied from 0.002" to 0.0075" and mostly lay between 0.003" and 0.005". The degree of summation was then about 0.1. After the

first ten, fifteen or twenty contractions this value had considerably decreased in most cases (experiments 20, 21, 22, 23, 26, 27, 28, 32 and 66) viz. to about half its original height, and in some cases (experiments 22, 23, 26) even to 0. Apart from numerous irregularities the degree of summation is likewise lowered by further stimulations but more slowly than at first, after a continued stimulation it became 0, for instance, in experiments 2, 4, 9, 20, 21, 24, 25. In 7 cases it became evident that an increased stimulation interval may cause summation again. The interval was lengthened

in N <sup>o</sup> . 4	from	0.002"	to	0.015"
" " 9	"	0.004"	"	0.008"
" " 20	"	0.0025"	"	0.0063"
" " 21	"	0.004"	"	0.005"
" " 23	"	0.003"	"	0.0056"
" " 25	"	0.0033"	"	0.0066"
" " 26	"	0.0033"	"	0.0054"

On the other hand there are likewise a rather great number of experiments (Nos. 1, 3, 13, 14, 17, 19, 64, 65) in which, mostly only at first, the degree of summation was heightened by stimulation. These changes were, however, as a rule much smaller than those mentioned above, while attempts to retain summation with smaller stimulation-intervals did not succeed.

It has not come to light, to what cause this instability in the consequences of the fatigue must be attributed. Those curve-series in which the decrease of the contraction-height, in other words the effect of the fatigue is most regular, (experiments 19, 20, 21, 23) likewise present a rather regular decrease of the degree of summation. Irregularities in the change of the contraction-heights mostly coincide with irregularities in the degree of summation. The decrease in the summation is most evident in those experiments in which fatigue considerably lengthened the *duration* of the contraction whilst its *height* almost remained the same (experiments 2, 4, 5, 6, 7, 8, 10); all these were carried out in March at a rather low temperature.

Hence the effect which fatigue may have on the duration of the refractory-stage, is a lengthening one.

#### *Temperature.*

In the following experiments the muscle was placed in a glass vessel, which in experiments 29 to 33 was filled with 0.7% NaCl-solution, while in experiments 34, 60, 61, 62, 63 it acted as a moist chamber. The muscle was fastened underneath to the short arm of the lever and made equilibrium with a weight of about 5 grammes.

For the rest the installation was the same as in the other experiments.

The following is experiment 62.

At 10° the degree of summation was 0.04, the stimulation-interval being 0.0047'. After refrigeration to 5° no summation set in at this

Number of the experiment	Temperature	Stimulation-interval	Contraction-height after one stimulation	Degree of Summation
29	20°	0.0027''	78 mm.	0.21 ?
	10°	"	54,7	0.021
	10°	0.0075''	50	0.07
	5°	"	49.5	0.037
	5°	0.013''	49.5	0.05
30	18°	0.0045''	57	0.14 ?
	13°	"	34.5	0
	8°	0.0117''	34	0.007
31	20°	0.0054''	39	0.18
	17°	"	27	0.18
33	21°	0.0018''	20	0.5
	10°	0.0063''	9,5	0.3
	10°	0.0018''	4.5	0.1
34	20°	0.0018''	27	0.43
	10°	"	20	0
60	20°	0.0022''	45	—
	20°	0.0042''	42	0.15
	10°	"	38	—
	10°	0.0063''	38	—
	10°	0.0095''	38	0.13
62	10°	0.0047''	49	0.04
	5°	"	46	0
	5°	0.0115''	46	0.05
	2°	0.0115''	53	0
	2°	0.021''	53	0.037

interval, nor at an interval of 0.0063", whilst lengthening to 0.0115" made the degree of summation 0.05. The muscle having been cooled down to 2° the summation was 0 at a stimulation-interval of 0.0115" and 0.0157", whilst it became 0.037 at an interval of 0.021".

The other experiments gave similar results (See page 1223).

Refrigeration therefore lengthens the refractory stage.

The temperature from which we started being an arbitrary one the effect of heating was also investigated.

From the following values

Number of the experiment	Temperature	Stimulation-interval	Contraction-height after one stimulation	Degree of summation
60	9°	0.005"	39 m.m.	0.05
	20°	"	47.5	0.5
	20°	0.0022"	47.5	0.03
61	9°	0.0053"	35.25	0.12
	26°	0.001"	77	0.117
63	8°	0.0078"	42	0.098
	22°	0.00105"	60	0.25
67	12°	0.0042"	42.75	0.05
	30°	0.0021"	83	0.096

it appeared that heating shortens the refractory stage.

#### *Carbonic acid.*

In the moist chamber, used in the foregoing experiments carbonic acid was led, for the rest the installation was the same. Though carbonic acid gas will act upon the muscle but very slowly from outside, it may yet be assumed that within not too long a time it will have a marked influence on the condition of the muscle, since it prevents the carbonic acid formed by function in the muscle, from leaving it.

The following is experiment 59.

At a stimulation-interval of 0.0042" the muscle originally gives a summation of 0.06. After having been surrounded by carbonic acid gas for 15', it shows no summation at this interval, whilst summation becomes 0.06 again, if the stimulus-interval is lengthened to 0.0068".

Remaining in the carbonic acid the muscle gives at intervals of 10' a summation of 0.046, 0.036, 0.035 and 0. Five minutes after, at a stimulus-interval of 0.0089" the degree of summation is 0.009. After 65', at an interval of 0.0115", the summation amounts to 0.019; ten minutes later, it is at this distance 0, for an interval of 0.0136" 0.015, for one of 0.0168" 0.03. 40 minutes after, after 115' the degree of summation becomes 0 also for this distance.

The values of the other experiments are the following:

Number of the experiment	Temperature	Exposure to CO <sub>2</sub>	Stimulation interval	Contraction-height after one stimulus	Degree of summation
43	13°	0	0.002"	28 m.m.	0.035
		10'	"	27.5	0.035
		20'	"	—	—
44	?	0	0.002"	29	0.55
		?	"	—	—
45	14°	0	0.002"	56.5	0.009
		10'	"	35.25	0.02
		10'	0.003"	35.25	0.02
		20'	0.002"	37	0
		20'	0.003"	32.5	0
		30'	0.002"	27.5	—
		30'	0.003"	20.5	0.1
46	14°	5'	0.0035"	62	0.024
		15	"	60	0.05
		25	"	57	0.026
47	17°	0	0.0033"	37.5	0.04
		10'	0.0066"	15	0.1
		10'	0.011"	15	0.17
48	11°	0	0.0055"	18	0.11
		5'	"	13	0.115
		10'	"	14.5	0
		15'	0.008"	13	0.08

Number of the experiment	Temperature	Exposure to CO <sub>2</sub>	Stimulation-interval	Contraction-height after one stimulation	Degree of summation
49	?	0	0.003"	50 m.m.	0.04
		10'	"	45	0.04
		20'	"	40	0.025
50	?	0	0.0022"	41.5	0.08
		0	"	45	0.08
		10'	"	50.5	0.05
		20'	"	53	0.038
		30'	"	53	0.075
		30'	"	56	0.027
		40'	"	54	0.027
		50'	"	50.5	0.03
		60'	"	52	0.03
51	12°	0	0.0018"	37	0
		0	0.0054"	33	0.035
		5'	"	49.5	0.01
		25'	"	48.5	0.01
		35'	"	46	0.022
		50'	"	45	0
52	16°	0	0.002"	60	0.033
		15'	"	64.5	0.05
		25'	"	54.5	0.12
		35'	"	54	0.13
53	13°	0	0.0063"	46.5	0.15
		30'	"	43.5	0.103
		45'	0.0063"	46.5	0
		45'	0.0084"	46.5	0.02
		45'	0.0157"	46.5	0.054
54	13°	0	0.0048"	54	0.074
		20'	"	55.5	0.117

Number of the experiment	Temperature	Exposure to CO <sub>2</sub>	Stimulation interval	Contraction height after one stimulation	Degree of summation
54	13°	30'	0.0048"	56 mm.	0.107
		50'	"	57.5	0.05
		60'	"	55	0.046
55	14°	0	0.00525"	34	0.03
		15'	"	23.5	0.04
		20'	"	19	0
		30'	"	—	0
56	6°	0	0.0054"	43	0
		?	"	23	0
		?	0.0072"	23	0
		?	0.0054"	20.5	0
57	12°	0	0.005"	40	0.04
		10'	"	35	0.03
		20'	"	33	0.03
		30'	"	32	0.03
		40'	"	32	0
		50'	—	—	?
58	8°	0	0.0066"	20.5	0.07
		10'	0.011"	26	0.019
		20'	0.014"	15	0.033
		30'	"	13.5	0.07
		40'	"	9	0.1
		40'	0.0088"	9	0
59	10°—13°	0	0.0042"	42	0.06
		15'	"	34	0
		15'	0.0068"	34	0.06
		25'	"	33	0.046
		35'	"	27.5	0.036
		45'	"	28	0.035

Number of the experiment	Temperature	Exposure to CO <sub>2</sub>	Stimulation-interval	Contraction-height after one stimulation	Degree of summation
59	10°—13°	55'	0.0068"	27.5 mm.	0
		60'	0.0089"	25.5	0.009
		65'	0.0115"	26	0.019
		75'	"	33	0
		75'	0.0136"	33	0.015
		75'	0.0168"	33	0.03
		90'	"	35	0.013
		100'	"	35.5	0.056
		115'	"	31.5	0

From this table it appears that if the muscle was surrounded for some time by carbonic acid, the degree of summation grew considerably less, and even fell in about half the cases to about 0 (experiments 45, 48, 51, 53, 55, 57, 58 and 59). Lengthening of the stimulation-interval often caused the summation to return as in experiments 48, 53, 58, 59. In some cases the degree of summation increased after carbonic acid had been led in for some time, viz. in experiments 46, 47, 52, 54 and 55; this was, however, mostly followed by a decrease. Also in this series of experiments a decrease in the summation, with an eventual necessity to lengthen the stimulation-interval, most clearly manifested itself, when the duration of the contraction grew much longer and its height did not decrease much.

From the foregoing experiments it appears that the refractory stage of the frog's gastrocnemius is lengthened by being cooled down, by carbonic acid and by fatigue, especially in those cases in which under these influences the contraction is protracted. In connection with this, the lengthening of the refractory stage most regularly sets in at refrigeration, whilst fatigue gives the most unstable results. This lengthening takes place in various degrees; mostly the stimulation-interval was at last from two to five times its original length, so that it may be assumed that the refractory stage was likewise changed to about that extent.

As regards the average length of the refractory stage, the values of the intervals used are of course somewhat greater, because the limit where summation only just takes place had mostly not been



exactly arrived at. The average of the stimulation-intervals was for

9°	0.006"
10°	0.0047"
11°	0.0039"
12°	0.0047"
13°	0.0034"
14°	0.0033"
18°	0.0045"
20°	0.003"
21°	0.0029"
22°	0.0036"
23°	0.003"
25°	0.0032"
26°	0.0036"

in which, though somewhat irregular because of the relatively small number of experiments, it is evident that this, and consequently also the refractory stage, is greater at a low temperature. After refrigeration or heating to a certain temperature, the values found become respectively greater and smaller than those above.

The average of the values is somewhat less than 0.004", so that the average value of the refractory stage of the frog's gastrocnemius must also be somewhat less than 0.004", which is 0.001" less than the value found by TIGERSTEDT for the latent period.

The figure represents the contraction curves of a muscle after it had been cooled down from 14° to 4°. At 14° the stimulation-interval still showing summation was found to be 0.003". At 4° stimulation with the same interval produces no summation: the contraction-curve caused by two stimulations (II) coincides with the contraction-curve after one stimulation (I). The interval was

lengthened to 0.0075", then to 0.017" without summation following (curves II' and II"). Lengthening to 0.028 gives curve II", in which the summation is plainly visible.