Physiology. — "*An investigation on the quantitative relation between vagus stimulation and cardiac action, on account of an experimental investigation of* Mr. P. WOLTERSON" [1]). By Prof. H. ZWAARDEMAKER.

(Communicated in the meeting of December 29, 1906).

The experiments were performed on Emys orbicularis, whose right nervus vagus was stimulated by means of condensator charges and non-polarising electrodes of DONDERS [2]), while auricle and ventricle were recorded by the suspension method. The mica-condensators had a capacity of 0,02, 0,2 and 1 microfarad, the voltage varied from a fraction of a volt to 12 volts, occasionally even more. From this the intensity of the stimulus was calculated in ergs (or in coulombs by HOORWEG's method). Only a part of this energy, passing through the nerve, when it is charged, acts as a stimulus. What part this is remains unknown, but it is supposed not to vary too much in the same set of experiments. In the typical experiments a summation took place of ten stimuli, succeeding each other in tempos of $^1/_2$ second; in particular experiments single stimuli or other summations were investigated. Of fatigue little evidence is found with our mode of experimenting, rather a somewhat increased sensitiveness of the vagus system towards the end of a set of experiments.

Stimulation of the right vagus produces in the tortoise in the first place lengthening of the duration of a cardiac period [3]), in such a way that in the second period, after a stimulus, starting during the cardiac pause, the diastolic half of the period is considerably retarded, while in some subsequent periods a decreasing retardation of the diastolic part of the period is noticed.

Then stimulation of the vagus causes contraction to become feebler, this phenomenon becoming gradually more distinct and reaching its maximum some periods after stimulation. This decrease of contractile power is primary, since it may also occur when any change in the automatic action is absent (e.g. when the stimulus consists of one condensator charge and when the left vagus is stimulated). Finally vagus stimulation as a rule produces slackening of the tonus, rarely tonic heightening. Changes in conductivity were only observed once.

---

[1]) For details we refer to the author's academical thesis, which will be published ere long.

[2]) Onderzoekingen Phys. Lab. Utrecht (3) Vol I p. 4, Pl. I, fig. 1, 1872.

[3]) The duration of a cardiac period is reckoned from the foot-point of a sinusal contraction or if this is not visible, of an auricular contraction, to the foot-point of the next following sinusal resp. auricular contraction.

The negative chronotropy holds good for sinus, auricle and ventricle to the same extent, the negative inotropy exists exclusively for the sinus and the auricle, is mostly positive for the ventricle, if it is found; the tonotropy is met with in auricle and ventricle.

A latent stage of the phenomenon, measured by the time-difference between vagus stimulation and vagus action, was always observed. It is smallest for the inotropy; already the first period often shows an enfeeblement of the contraction, which in the subsequent periods increases still further. The latent stage of the chronotropy is greater, for only in the second, sometimes in the third period, a retardation is noticeable; on the other hand this phenomenon reaches its maximum at once. Inotropy and tonotropy do not coincide. On the contrary, the maxima of effect form the following series as to time: first maximum of chronotropy, then maximum of tonotropy, finally maximum of inotropy.

In regard to the sensitiveness for vagus stimuli, we remark that for the inotropy the "threshold value" lies below that for the chronotropy and for this latter lower again than for the tonotropy. So we have:

Threshold value for inotropy $<$ idem for chronotropy $<$ idem for tonotropy.

From the fact that dromotropy did not occur in our experiments, one would infer that the threshold value of the dromotropy lies higher still in the present case.

Physiologists are generally convinced that the rhythmic processes at the bottom of the cardiac pulsations, are based on chemical actions in the cardiac muscle. Leaving apart the founder of the myogenic theory TH. W. ENGELMANN, we mention some authoritative writers, FANO and BOTAZZI in RICHET's Dictionnaire and HOFMANN in NAGEL's Handbuch, who embrace this point of view [1]).

Also experimental results may be adduced in support of this theory. SNYDER [2]) showed that the frequency of the contractions with respect to temperature follows exactly the law, formulated by VAN 'T HOFF and ARRHENIUS for chemical reactions [3]) and experiments, independently made by J. GEWIN, entirely confirmed this. [4]) Whereas the influence of temperature is considerable, that of pressure is very small. This agrees with the small significance of external pressure for so-called condensed systems, i. e. systems in which no gaseous phases occur.

---

[1]) FANO and BOTAZZI, RICHET's Dict. de physiologie t. IV. p. 316.

[2]) SNYDER, Univ. of California Publications II. p. 125. 1905.

[3]) E. COHEN, Voordrachten. Blz. 236 1901.

[4]) J. GEWIN, Onderzoekingen Physiol. Lab. Utrecht (5). Dl. VII, p. 222.

For the automatism it seems to me to be settled, that it must be based on chemical processes.

For the remaining cardiac properties: conductivity, local sensitiveness to stimuli, contractile power and tonicity the decision is more difficult. The law of VAN 'T HOFF-ARRHENIUS concerning the relation between reaction-velocity and temperature can only be applied if the duration of the reaction is known. Now the velocity of conduction, measured with this purpose, increases with temperature up to a certain optimum [1]) whereas correspondingly the duration of the contractions is diminished [2]). The local excitability, however, has not been studied yet from this point of view, while also for the contractile power the time factor is still lacking. But the contraction of a muscle and also that of the cardiac muscle is so universally considered a truly chemical process, that the reader will not object to classing it among chemical phenomena without further arguments. As to the tonicity we are absolutely in the dark, although we know that rise of temperature chiefly brings about a change, in which the tonus is definitely abolished.

In preparing his thesis Mr. WOLTERSON had chiefly to deal with:

1. changes in the automatism (chronotropy);
2. changes in the contractile power (inotropy).

Both these changes are purely chemical phenomena, as was shown above.

For chemical processes the law of GULDBERG and WAAGE holds [3]), and we may apply this law to the processes here dealt with. For this purpose we shall have to give a nearer definition for our special case of the conception "times of equal change".

By "times of equal change" we mean the times in which a definite reaction has taken place between two accurately fixed and in the corresponding cases analogous terminal points. The total duration of a cardiac period is such a characteristic time element, the beginning and end of which cannot be determined with the balance after chemical analysis, but still are determined by biological characteristics. The time between the beginning and the end of a cardiac period may be looked upon as a time of equal change provided no

---

1) TH. W. ENGELMANN. Onderz. Physiol. Lab. Utrecht (3d series) III p. 98. Above the optimum the conductive velocity diminishes again.

2) HOFMANN l. c. p. 247. Recently confirmed by V. E. NIERSTRASZ; vide acad. thesis, Utrecht 1907, p. 145, fig. 22: a fall in temperature of 9° gave an increase of the duration of the systole to the double value.

3) E. COHEN. Ned. Tijdschr. v. Geneesk. 1901, Vol. I, p. 58. Cf. also ZWAARDEMAKER, ibidem, 1906. Vol. II. p. 868.

inotropic changes occur [1]) and the mechanical resistance which the heart has to overcome, has remained the same.

These premisses made, we may at once apply the fundamental equation of GULDBERG and WAAGE's law;

$$\varphi = kC^n$$

Here k is a constant, the constant of the reactional velocity, C is the quantity of the substance, taking part in the reaction, n is the exponent, determining the so-called order of the reaction, while φ indicates the reactional velocity. About the exponent n nothing can be stated a priori for the heart. Toxicological experiments, in which the quantity of the reacting substance diminishes, might perhaps teach us something in this respect; perhaps also experiments on fatigue might give us some clue; at present, however, no data at all are available. Whether there are intermediate reactions and in what number, cannot be ascertained. Under these circumstances I assume, quite arbitrarily, that the present case is the simplest and that the exponent is unity. If later this assumption turns out to be wrong, our calculations will still apply, mutatis mutandis, without losing their meaning. In this simple case the formula runs:

$$\varphi = k\,C.$$

When the vagus is stimulated a very marked alteration of the times of equal change is noticed. The reactional velocity of the hypothetical chemical process, which lies at the bottom of the automatism, must consequently undergo a very considerable change. Such a change cannot take place unless either k or C are modified. In the literature on the subject both views are put forth, but only the conception that k changes, leads to a clear explanation without further auxiliary hypotheses. It also fits in best with a recent paper of MARTIN [2]), according to which vagus-inhibition is ascribed to the action of K-ions and is counter-acted by rise of temperature. The significance of the ions of the alkalies and alkaline earths for the cardiac muscle is indeed by no means fully explained, even after the numerous investigations of J. LOEB and his followers and critics — they are regarded by some as the cause of the continually excited condition of the cardiac muscle, as the stimulus for the automatism [3]), by others as the condition, necessary for keeping the

---

[1]) In the ventricle vagus-stimulation produces no inotropy.

[2]) MARTIN. Amer. Journal of Physiol. Vol. XI, p. 370, 1904 (MARTIN himself seems to assume a compound of K-ions with C).

[3]) WENCKEBACH. Die Arythmie etc. Eine physiol.-klinische Studie. Leipzig. 1904.

active substances in solution [1]) — they certainly do not enter into simple chemical combination with the cardiac substance, by which this latter would become unfit. If this latter were the case, the life-prolonging influence of RINGER's solution and the remarkable antagonism of *Na* and *K* on one hand and *Ca* on the other, would be entirely unexplainable.

By placing the principal weight on the hypothesis that the vagus alters the constant of velocity, of reaction we were led to the application of the formula for the catalytic acceleration of a chemical reaction. The catalytic acceleration is here negative. The explanation of the formula will be found in G. BREDIG's work. It runs:

$$\beta = k' - k = \frac{1}{(t'_2 - t'_1)} - \frac{1}{(t_2 - t_1)}.$$

By application to our experiments, the normal duration of the period being indicated by $(t_2 - t_1)$ the altered one during the principal retardation by $(t'_2 - t'_1)$, a relation became evident which appears to be constantly found between the intensity of the vagus stimulus on one hand and the retardation, indicated by β on the other. (An examination of the curves, recorded by the heart would show that the retardation affects principally the diastolic part of the process, but since for this part, taken separately, the times of equal change cannot be sharply determined, our calculations enclose the whole process).

When the vagus stimulus increases the retardation increases also very gradually, until a definite degree is reached; from this moment the reactional velocity of the hypothetical process of the automatism remains the same, independent of any rise in the intensity of the stimulus. Only by increase of the duration of the vagus stimulus, a new retardation may be produced, which is pretty well proportional to the extension of the duration of the stimulus. For a warmed heart all this holds without any alteration.

---

[1]) H. J. HAMBURGER. Osmotischer Druck und Ionenlehre. Bd. III, p. 127.

Exp. 8, VI. 1906. Emys orbicularis. Right nervus vagus stimulated on non-polarising electrodes with charging currents. Capac. of the condensator 1 microfarad. Number of stimuli 10 (2 per second). Between the series of stimuli pauses of 4 minutes; external temperature 18° C.

Micro-coulomb	Ergs	Initial retard. in %	Total retard. in %	β
0.80	3.20	13	23	—0.0392
0.82	3.36	92	143	—0.1662
0.84	3.53	95	133	—0.1694
0.86	3.69	282	347	—0.2555
0 88	3.87	320	385	—0.2716
0.90	4.05	320	364	—0 2635
0 92	4.23	322	360	—0 2648
0 94	4.42	346	364	—0.2765
0 96	4.61	337	366	—0.2575
0.98	4.80	337	398	—0.2667
1.00	5 00	343	398	—0.2679
1.04	5 41	333	394	—0.2570
1.08	5 83	346	410	—0.2765
1.12	6.27	333	367	—0.2661
1 20	7.20	330	322	—0.2480
1.28	8.19	346	373	—0.2592
1.36	9.25	336	370	—0.2575
1 52	11 50	343	374	—0 2679
1.68	14.11	360	421	—0.2790
1.84	16.93	340	377	—0 2673
3.68	67.71	371	405	—0.2723
5 52	152.35	371	418	—0.2723
7.36	270.85	371	411	—0.2723
9.20	423.20	357	377	—0.2702
11.04	609.40	333	347	—0.2661
0.80	3.20	330	343	—0.2654

Exp. 15, VI. 1906. Emys orbicularis, Right nervus vagus. Non-polarising electrodes. Charging currents. Capac. 0.2 microfarad. Number of stimuli 10; (2 per second). Resting pauses between the series of stimuli 2 minutes. Experimental animal in 0.6% Na Cl solution, heated to 28° C.

Micro-coulombs	Ergs	First visible retardation noticeable in the second period of the stimulus in %	2nd idem in the 3rd period	Total retardation	β col. 3	β col. 4
0.48	5.76	13	139	224	—0.0785	—0.3889
0 496	6 15	20	99	155	—0.1111	—0.3334
0 504	6 35	20	139	205	—0.1111	—0.3889
0 52	6 76	26	152	224	—0.1404	—0.4035
0.552	7.61	26	152	224	—0.1404	—0.4035
0.616	9.48	26	152	218	—0.1404	—0.4035
0 744	13 83	28	199	270	—0 1587	—0.4762
1 116	31 13	21	157	270	—0.1261	—0.4579
5 58	155 65	28	157	284	—0.1587	—0 4579

Two particulars deserve notice:

1. that the greatest retardation falls not in the second but in the third period.

2. With stimulation with 7,61, 9,48, 13,83 ergs turbulent motions occur in the ventricle, followed by the post-undulatory pause, namely in the first systole after the preliminary retardation.

The relation brought to light in both these cases might be explained by assuming with LANGLEY that the vagus fibres do not reach the heart directly, but first pass a station of the intra-cardial ganglia. If this be the case the stimulated condition of the prae-ganglionic fibres will only be communicated to the post-ganglionic by contact in the ganglion cells. But then the quantitative coercion of WEBER's law holds for these ganglion cells and a relation as sketched above is not astonishing. To this conception may be objected that probably with stimulation of the post-ganglionic fibres (in the so-called n. coronarius [1]) the same relation will be found in its principal features. If on this point not only preliminary, but decisive experiments will have been made, it will be found that the just-mentioned explanation

[1]) On the n. coronarius as a post-ganglionic nerve vide J. GEWIN, l. c. 82.

is untenable. Mr. WOLTERSON accordingly gives an alternating explanation which, in my opinion possesses some probability, and which agrees with MARTIN's hypothesis on the nature of the vagus action.

Let us suppose that by the action of the vagus some catalytic substance — say MARTIN's *K*-ions — is produced in the receptive substance of the cardiac muscle, then the above stated quantitative relation will be explained, if we may assume that the substance, produced by vagus action, is only to a limited extent soluble in the medium. For with a small production of the catalyser this latter will be dissolved and will increase the retardation, but when the medium has become saturated with the catalyser, further secretion is without effect. It must further be assumed that the newly formed catalyser is at once removed from the substance by diffusion or is deposited in the form of indifferent compound, for the vagus action is known to cease after a short time. Only when the duration of the stimulus is increased and catalytic substance is again and again produced, the disappearance of the catalyser may be compensated and the retardation may be lasting.

The second chemical process we meet in Mr. WOLTERSON's thesis, that of the contractility, cannot be submitted to the above followed treatment, since the time-factor is wanting. We tried to introduce this latter by seeking the relation between the intensity of the vagus stimulation and the duration of the inotropic action, but this latter is not itself a chemical reaction, but only a modification of the conditions under which periodically recurring reactions take place. The negative inotropy may at the utmost be regarded as a diminution of the quantity C in the formula $\varphi = kC$, which amounts to the assumption that by vagus stimulation the quantity of the just mentioned substance, undergoing chemical change, is diminished. But this also is uncertain, for in the chemical reaction of the automatism C represents part of LANGLEY's receptive substance, which is different from the contractile substance. So I prefer to keep the two chemism apart and to consider the inotropy entirely by itself.

Placing ourselves on this point of view, we notice: 1. that with feeble and increasing vagus stimuli the inotropic effect on the sinus and auricle gradually increases with the intensity of the stimulus, until a certain degree of inotropy has been reached, after which it does not increase further for any intensity of the stimulus; 2. that an analogous relation holds good for the duration of the inotropic effect; 3. that the pessimum of contractility is found about the end of the first third or fourth part of the total duration, for which the inotropy exists.

Summarising we arrive at the following conclusions:

A. the chronotropy, produced by stimulation of the vagus, may be reduced to a negatively catalytic action on a chemical process which lies at the bottom of the pulsation.

B. the inotropy admits by analogy of a similar interpretation, but it is impossible to prove this, since at present no times of equal change can be determined here.

As secondary results we mention:

a. the existence of twofold negatively chronotropic fibres in the right vagus of the tortoise.

b. a particularly great sensitiveness of the heart of the tortoise for inotropy of the auricle by vagus stimulation, in such a degree that a single condensator discharge may produce the stated modification and that also with cumulative stimulation it appears sooner and lasts longer than the chronotropy.

c. the occasional occurrence of spontaneous cardiac turbulence in a warmed tortoise heart, immediately after a principal retardation brought about by vagus stimulation.

E R R A T U M.

In the Proceedings of the meeting of December 29, 1906.

p. 504, line 13 from the bottom: for 2 read 4
p. 511, line 5 from the top: for 0.052 read 0.104

(February 21, 1907).

KONINKLIJKE AKADEMIE VAN WETENSCHAPPEN TE AMSTERDAM.

PROCEEDINGS OF THE MEETING

of Saturday February 23, 1907.

(Translated from: Verslag van de gewone vergadering der Wis- en Natuurkundige Afdeeling van Zaterdag 23 Februari 1907, Dl. XV).

CONTENTS.

A. P. N. FRANCHIMONT: "Contribution to the knowledge of the action of absolute nitric acid on heterocyclic compounds" p. 600.

F. A. H. SCHREINEMAKERS: "On a tetracomponent system with two liquid phases", p. 607.

J. BOESEKEN: "On catalytic reactions connected with the transformation of yellow phosphorus into the red modification". (Communicated by Prof. A. F. HOLLEMAN), p. 613.

J. D. VAN DER WAALS: "Contribution to the theory of binary mixtures", p. 621. (With one plate).

PH. KOHNSTAMM: "On the shape of the three-phase line solid-liquid-vapour for a binary mixture". (Communicated by Prof. J. D. VAN DER WAALS), p. 639.

PH. KOHNSTAMM: "On metastable and unstable equilibria solid-fluid". (Communicated by Prof. J. D. VAN DER WAALS), p 648. (With one plate).

W. H. KEESOM: "Contributions to the knowledge of the ψ-surface of VAN DER WAALS. XIII. On the conditions for the sinking and again rising of a gas phase in the liquid phase for binary mixtures". (Continued). (Communicated by Prof. H. KAMERLINGH ONNES). p. 660.

H. KAMERLINGH ONNES and Miss T. C. JOLLES: "Contributions to the knowledge of the ψ-surface of VAN DER WAALS. XIV. Graphical deduction of the results of KUENEN's experiments on mixtures of ethane and nitrous oxide", p. 664. (With 4 plates).

P. NIEUWENHUYSE: "On the origin of pulmonary anthracosis". (Communicated by Prof. C. H. H. SPRONCK), p. 673.