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Physiology. — "*Contribution to the knowledge of the influence of digitalis on the frog's heart. Spontaneous and experimental variations of the rhythm.*" By Dr. S. DE BOER.[1]) (Communicated by Prof. Dr. G. VAN RIJNBERK).

(Communicated in the meeting of November 25, 1916.)

I. *Introduction.*

It has been proved by a long series of investigations into the influence of digitalis on the frog's heart, that as a first result of the poisoning a slackening of the palpitation sets in, which is not a consequence of a stimulation of the Vaguscentra, as paralysis of the extremities of the Vagus through atropine does not prevent this slackening. It was moreover found that an increase of the size of the systoles sets in after the poisoning. In the second stage of the poisoning an irregular activity of the heart occurs, followed by a stagnation of the ventricle in a maximal condition of contraction. Afterwards the stagnation of the auricles follows.

BÖHM[2]) discovered that after the poisoning of the frog's heart with digitalis the systolic emptying increases in completeness, so that at the highest point of the systole the ventricle is white, a proof that the contents have been removed to the last drop. Suddenly the number of palpitations can be reduced to half the usual number, a halving of the rhythm of the ventricle, which is still repeated once or twice, till at last the ventricle stands still in systole. Then the auricles still continue to pulsate for a considerable time. BÖHM ascertained moreover that the irregularities of the heart-rhythm caused by poisoning with digitalis, disappear by stimulation of the Vagus.

WYBAUW[3]) obtained similar phenomena after poisoning with helleboreine: decrease of the frequency of palpitation, increase of the volume of palpitation and the activity of the heart in the first stage of poisoning; during the second stage of this process irregularities took likewise place, till at last the heart stood still in systole.

After washing the poison out the phenomena of poisoning could recoil again, whilst repeated poisoning occasioned a repetition of these phenomena.

By HEDBOM[4]) and STRAUB[4]) similar disturbances of rhythm of the

[1]) This investigation was made in the Physiological Laboratory at Amsterdam.
[2]) PFLÜGERS Archiv. Bd. 5.
[3]) Archiv f. exper. Pharmakol. Bd. 44.
[4]) Archiv f. exper. Path. u. Pharm. Bd. 45, 1901, Seite 317.
[5]) Archiv f. exper. Path. u. Pharm. Bd. 45, 1901, Seite 346.

frog's heart were found after poisoning with antiarine. STRAUB ascertained moreover that the duration of the refractory stage of the ventricle increases after the poisoning with antiarine. STRAUB indicates this prolongation of the refractory stage as the cause of the halving of the rhythm.

The prolongation of the refractory stage after poisoning with digitalis was ascertained by BRANDENBURG. [1])

The action of the specimens of the digitalisgroup corresponds consequently in many regards with that of veratrine. Both with digitalis- and veratrine-poisoning we find a decrease of the frequency of palpitation, an increase of the size of the systole, a prolongation of the refractory stage, which causes the disturbances of rhythm. The image of poisoning of the two poisons shows however still important differences.

II. *My own experiments.*

A. Method.

Specimens of Rana Esculenta served as trial-objects. The heart was suspended in the usual manner by attaching the point to a lever. Care was taken that during the stripping and the preparation of the heart the frog lost as little blood as was possible. The oscillations of the heart were registered by the lever on an endless smoked paper (circumference 2 m.) and enlarged 15 times. Under the curves of the heart a line was drawn through the stimulation-signal. This indicated the moment at which one of the partitions of the heart was stimulated. A downward movement of the signal was brought about by closing the primary circuit of the induction-apparatus. The closing induction strokes were blended off. The opening of the primary circuit caused an upward movement of the signal. The opening induction-strokes were conducted only to the preparation. Under the line of the stimulation-apparatus the time was registered in seconds. Three series of experiments were made. In the first series the irritability of the auricle before and after the injection of digitalis was ascertained. In the second series the same experiments were applied to the point of the ventricle, in the 3rd series to the basis of the auricle. About 200 systoles were always registered before the injection with digitalis. Then 10—15 drops of digitalis dialysatum Golaz were injected under the skin of the thigh.

After the poisoning the curves were registered during several hours on the smoked paper. In this way I obtained a survey of

[1]) Archiv. f. Physiol, Jahrg. 1904. Suppl.

the process of the poisoning, and at the same time I could study the heart in the various stages of poisoning by applying extra-stimulations.

B. The image of poisoning with digitalis.

If we speak of the image of poisoning that we observe with a frog's heart after injection of digitalis, then we understand by it the reaction of the heart on such a dose as occasions disturbances of the rhythm and in the end stagnation of the heart. We can arrange this image of poisoning into 3 stages.

1. The beginning of the poisoning in which the undisturbed normal rhythm still continues, i.e. every impulse of the sinus venosus is answered by all the partitions of the heart with a contraction. 2. Stage of the disturbances of the rhythm. This stage often begins with an alternation of the ventricle which thereupon is converted into halving of the rhythm of the ventricle or formation of groups, afterwards often alternation of the halved ventricle-systoles, then further halving of the ventricle-rhythm. The halving of the auricle-rhythm sets in later than the halving of the ventricle-rhythm. 3. Stage of the groups of Luciani, usually converting into separate ventricle-systoles e. g. to about 16 auricle-systoles 1 systole of the ventricle. Then follows a stagnation of the ventricle. These are the 3 stages of the image of poisoning, as it shows itself in the ventricle. After the stagnation of the ventricle the auricles still continue to pulsate either in the normal or in the halved rhythm or in bigeminus-groups, whilst frequently variations in these rhythms occur.

1. *First stage.* The frequency of the palpitation of the heart slowly decreases. The systolic emptying of the ventricle becomes more complete. We see the ventricle contract during the systoles to a small white ball. The duration of the $a—v$ interval increases, towards the end of this stage the height of the systoles decreases remarkably. We observe at the same time a distinct decrease of the irritability of the muscle of the ventricle. Stimulations that before the injection, in the beginning of the diastole, caused an extra-systole, must after 15 minutes be either fortified or be applied later in the heartperiod in order to have the same result. Fig. I represents the suspension-curves of a frog's heart in the first stage of the poisoning. At 1 an extra-stimulation is applied to the basis of the ventricle towards the end of the diastole. No extra-systole of the ventricle takes place, but the auricle shows an extra-systole. During the compensatory pause the stimulation is repeated at 2, but at a moment at which

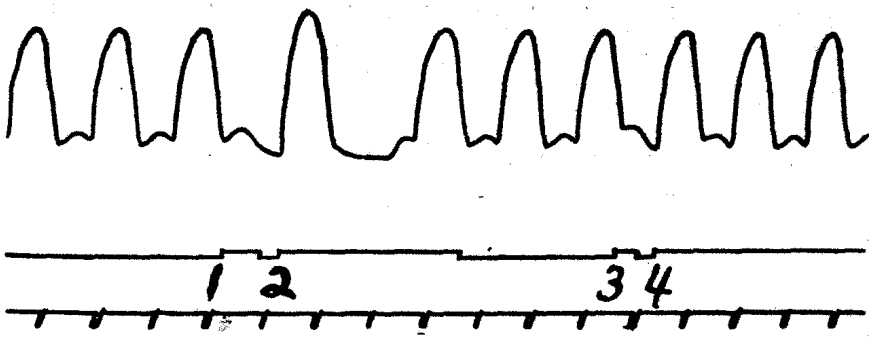

Fig. 1.

the ventricle continuing to pulsate when undisturbed, would not have passed into systole. Therefore this extra-systole is followed by a compensatory pause.. When at 3 and 4 I repeat the same experiment, but apply now at 4 the 2nd extra-systole with a slight scope at a moment, when in normal circumstances the ventricle would likewise have produced a systole, an extrasystole occurs that is not followed by a compensatory pause. As before the injection with digitalis a slighter stimulation on the basis of the ventricle in the beginning of the diastole promptly caused an extra-systole of the ventricle, this fact proves clearly the decrease of the irritability of the muscle of the ventricle. At the same time this experiment teaches us, that an extra-systole of the ventricle is only followed by a compensatory pause, when the extra-systole falls entirely beyond the physiological period of stimulation.

In different ways the first stage can pass into the 2nd. As a rule the rhythm of the normal equally high systoles passes into alternation. The large systole of an alternation-pair is then greater, the little one smaller than the systoles of the normal rhythm. In Fig. 2 such a transition is represented. Fig. 3 shows an alternation, in which the little systole sets in retardedly, on account of a distinct prolongation of the $a—v$ interval. This causes the distance between the beginning of a great ventricle-systole and the beginning of the next following little ventricle-systole to become considerably greater than the distance between a little systole of the ventricle and the next following great one.

Now the alternation lasts very short, now longer, and passes then into halving of the rhythm of the ventricle. It occurs likewise that the alternation does not set in at all, so that then the normal rhythm of the ventricle passes directly into the halved rhythm or into formation of groups, as I described circumstantially after poisoning with veratrine.

2. *Second stage.* Consequently the 2nd stage begins usually with

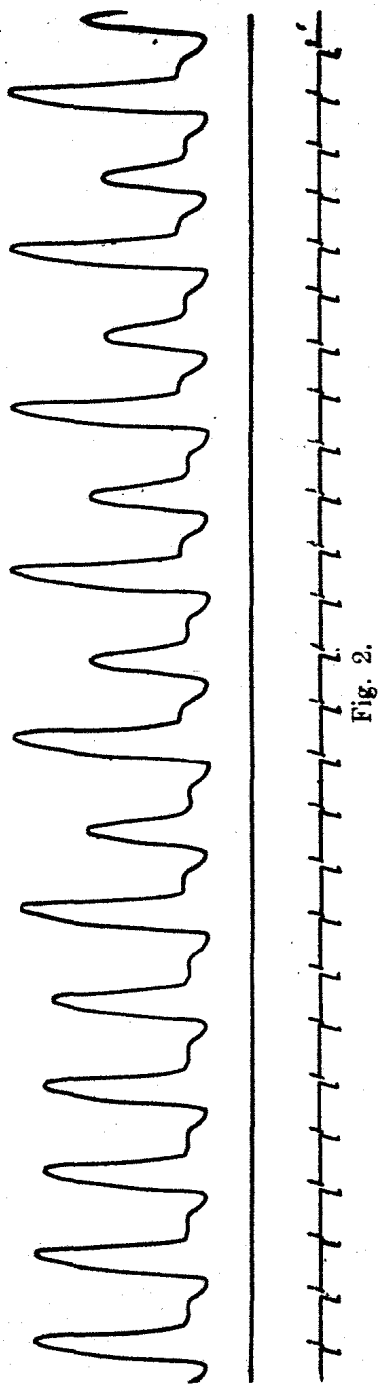

Fig. 2.

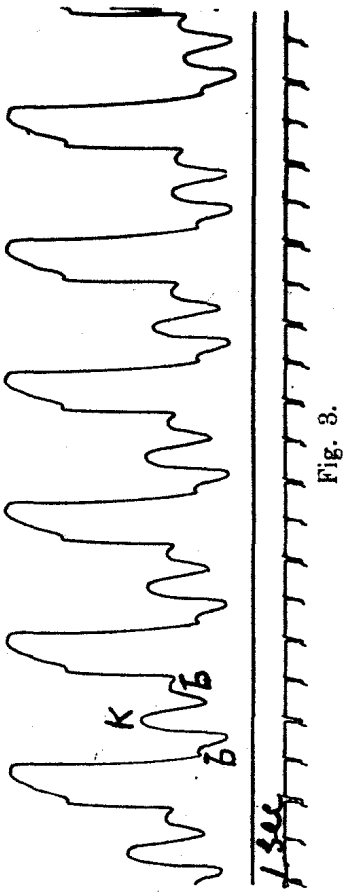

Fig. 3.

alternation of the ventricle. This alternation was likewise described by MUSKENS [1]) and BRONDGEEST [2]). Gradually the height of the little

[1]) These Proc. X p. 78.

[2]) Nederl. Tijdschr. v. Geneesk. 2e reeks jaarg. 39. Vol. I, 1903, p. 1294.

curves of the alternation decreases, after which the halved rhythm of the ventricle sets in. In this halved rhythm of the ventricle alternation followed by a further halving can likewise set in again. The rhythm of the auricle halves later than that of the ventricle. The halved rhythm of the ventricle is often not complete. After the systoles of the auricle, succeeding the systoles of the ventricle, the ventricle is entirely filled with blood, and at the same time repeatedly

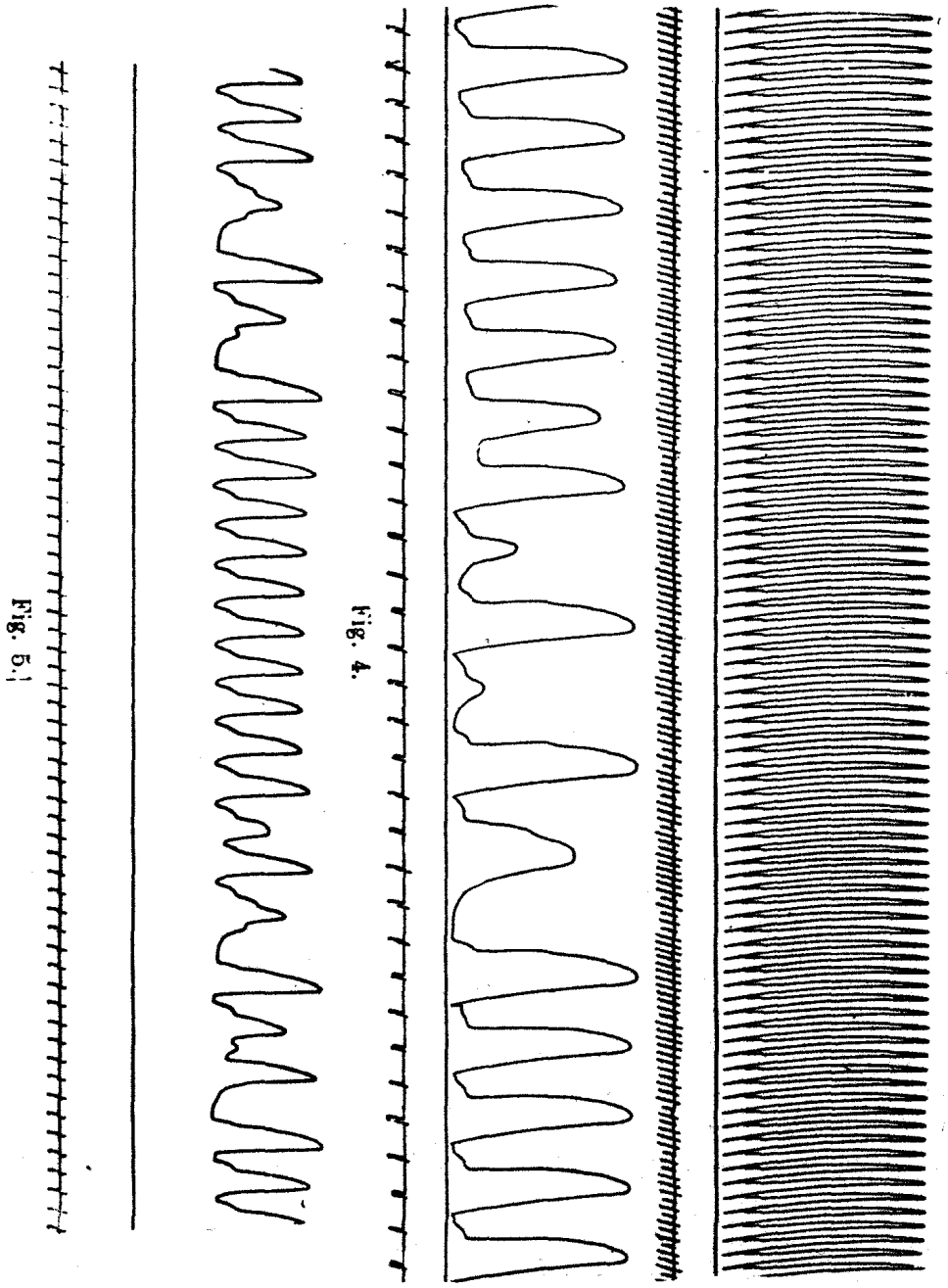

Fig. 5.

Fig. 4.

very small contractions, abortive systoles of the muscle of the ventricle, take place (vide Fig. 11 at the figures 2). I observed this phenomenon so often that I should naturally be inclined to suppose a connection between the occurrence of the small contractions of the ventricle and the considerable filling with blood of the ventricle. My supposition in this respect was supported by the fact, that I did not observe this phenomenon after the poisoning with veratrine, when the filling of the ventricle with blood decreases considerably [1]).

Besides the mentioned disturbances of the rhythm of the ventricle we observe in this stage still considerable disturbances in the conductivity of the ventricle. This can cause the systole to increase considerably in width (vide Fig. 4th lower row of curves). But it can likewise cause a great difference in the shape of the curves of the systoles and make them deviate entirely from the normal ones.

Many types of these can be observed, some of them I shall describe here. In the first place the ascending line of curves can show a distinct inclination (Fig. 5). Then the top can be split (Fig. 6) and finally a new ascent of the curves can occur in the dilatation (Fig. 7). This 2nd ascent can obtain a greater height than the first top (Fig. 8 and Fig. 13). The postulation could be made that extra-systoles are at work with these curves, but several data tell against this conjecture.

In the first place the fact that the new ascent can occur during the stage of contraction, tells against it, and at the same time the fact that the 2nd ascent during the diastole can by far exceed the first in height. We have here consequently no coordinated systoles of the ventricle.

We often see that these deformed systoles exercise a regulating influence on the rhythm of the systoles of the ventricle. A previously existing alternation afterwards often passes into systoles of the ventricle of equal height. (vide Fig. 4, 5, 6 and 7). We must find the explanation of this phenomenon in the prolonged pause, following after these deformed systoles. This one prolonged pause restores the muscle of the ventricle so much, that during some time normal systoles can follow. The prolonged pause after the deformed systoles owes its existence to the fact that on account of the increase of duration of these systoles the next following impulse coming from the auricle, reaches the ventricle during the refractory stage so that one systole of the ventricle falls out.

The following experiment shows distinctly that one prolonged

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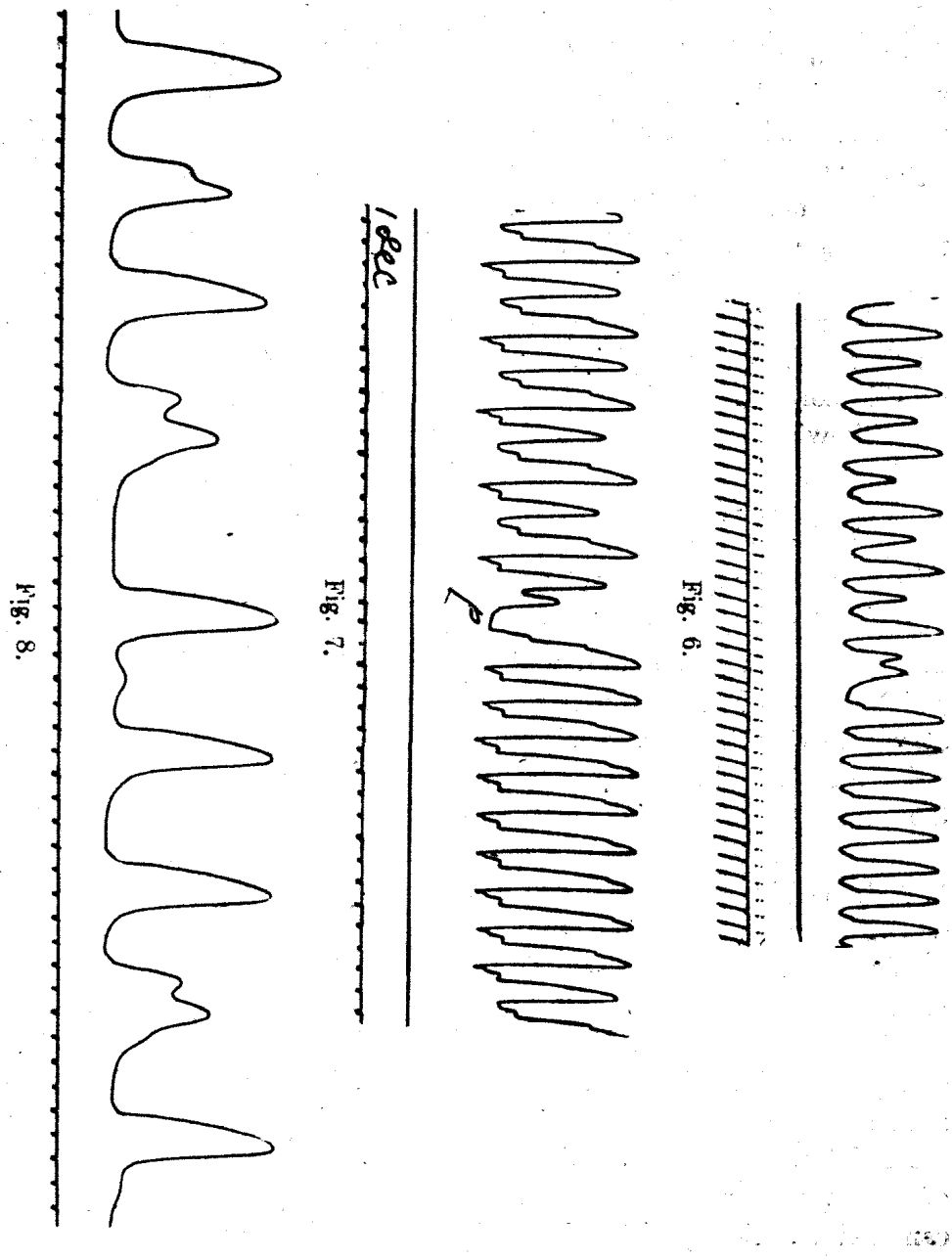
[1]) The increase of the filling of the heart after injection of digitalis is evidently caused by the concommitting vasoconstriction.



pause can regulate an alternation to the normal rhythm with equally high systoles. When a heart pulsates in alternation, I apply an extra-stimulation to the auricle or to the basis of the ventricle at the end of the diastole (Fig. 9). We can then obtain an extra-pause without extra-systole of the ventricle. This extra-pause is then followed by systoles of the ventricle, which obtain an equal height. In this way in Fig. 9 at 1 an extra-stimulation was applied to the basis

of the ventricle at the end of the diastole. Because the muscle of the ventricle is still refractory, no extra-systole of the ventricle takes place, but by current-loops the auricle is incited to extra-contraction. In this way the extra-pause occurs without extra-systole of the ventricle, and thereupon we see 9 systoles of equal height. Then the alternation sets in again, which is in the same manner transferred again into the normal rhythm of the ventricle by an extra-stimulation.

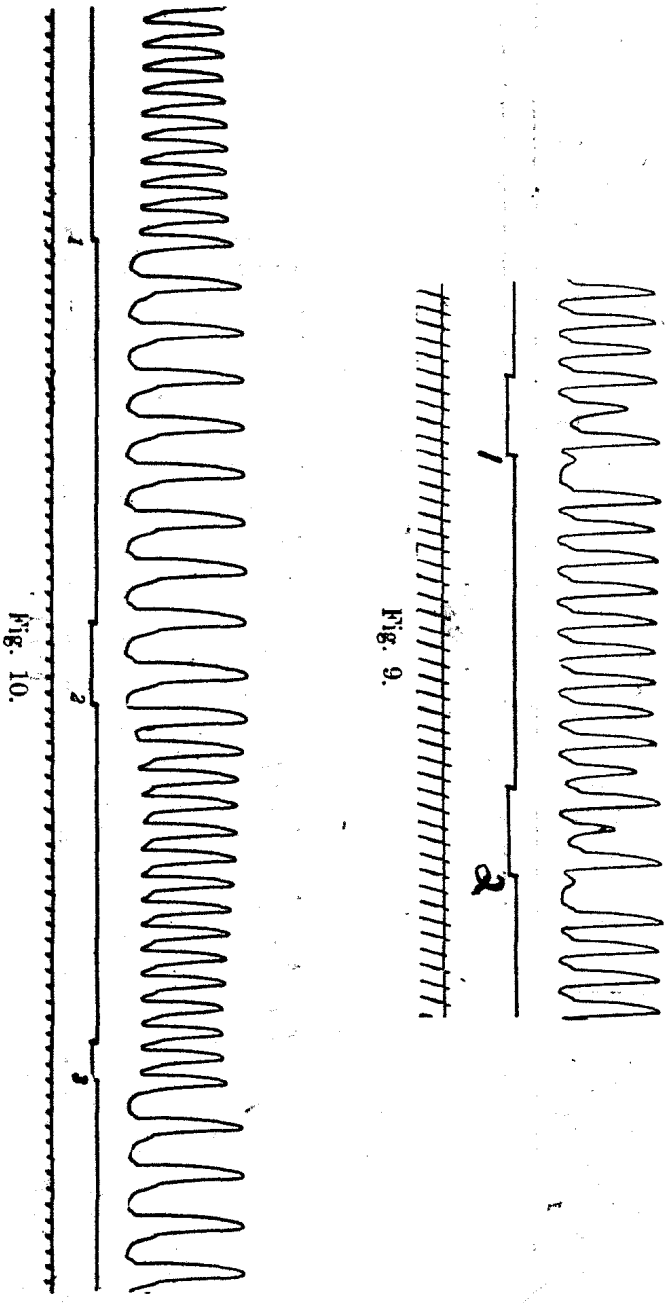


Fig. 10.

Fig. 9.

The alternation of the ventricle is usually followed by the halved rhythm of the ventricle.

We see this last rhythm repeatedly return spontaneously to the normal twice as quick rhythm. Other variations of rhythm occur likewise e. g. between the normal rhythm of the ventricle and bige-minusgroups (in which every third systole of the ventricle has fallen

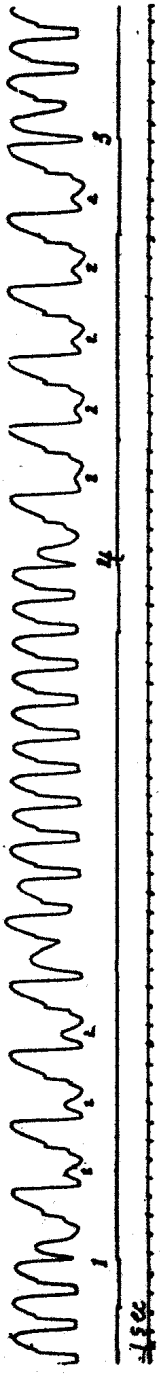


Fig. 11.

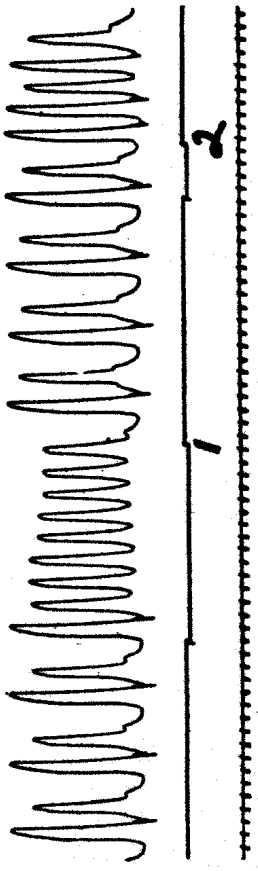


Fig. 12.

out) further between bigeminusgroups and the halved rhythm of the ventricle. *These variations of rhythms, which can occur spontaneously, I could likewise bring about experimentally.* A few examples may follow here.

In Fig. 10 I apply at 1 during the 10_{th} systole an extra-stimulation to the basis of the ventricle at a moment at which the ventricle is still refractory. By current-loops the auricle is incited to an extra-contraction, after which an extra-pause follows. The next following systole of the ventricle has considerably increased after the prolonged pause, by which the ventricle is fastened in the halved rhythm. By means of a succeeding extra-stimulation at 2 at the end of the pause this halved rhythm of the ventricle is changed again into the normal one. At 3 I change this normal rhythm of the ventricle again into the halved one.

In fig. 11 we see the representation of the curves of another poisoned heart. During the first 3 curves of the figure the heart pulsates in the normal rhythm of the ventricle. At 1 I apply an extra-stimulation to the point of the ventricle, which causes a little extra-systole. The postcompensatory systole is much enlarged. Then 3 more of these enlarged systoles follow, but each of these enlarged systoles is followed by a very slight contraction of the ventricle which varies a little in size (indicated by the figures 2). We have here consequently the halved rhythm of the ventricle with this reservation, that every systole of the ventricle is still followed by a slight contraction of the muscle of the ventricle. This rhythm of the ventricle passes spontaneously into the normal one. At 4 I modify this normal rhythm, in the same way as at 1, by an extra-stimulation into the halved rhythm of the ventricle (at the figures 2 again slight contractions of the ventricle occur). At 3 I apply again at the end of the diastole an extra-stimulation to the point of the ventricle. A little extra-systole with a refractory stage of short duration is the result. The normal rhythm of the ventricle is restored by it.

Fig. 12 represents curves of a frog's heart after poisoning with digitalis. In the figure we see first 3 bigeminusgroups occasioned by the falling out of every 3^{rd} systole of the ventricle. These bigeminousgroups pass spontaneously into the normal rhythm of the ventricle. At 1 an extra-systole of the auricle not followed by a systole of the ventricle occurs after an extra-stimulation of the auricle. Under the influence of the prolonged pause the next following systole of the ventricle is now considerably enlarged, the consequence of this is, that now bigeminousgroups set in. By an extra-stimulation to the auricle in the pause between 2 groups at 2 this bigeminy is

modified into the normal rhythm of the ventricle. A more explicit explanation of these artificial modifications of rhythm can be found in the communication dealing with the artificial modification of rhythm after the poisoning of a frog's heart with veratrine [1]).

If now we restrict our discussion to the ventricle, we have during the 2nd stage of the poisoning the following modifications:

1. Halvings of rhythm
2. Formation of groups.
3. Alternation.
4. Deformed systoles (often with more than 1 top).
5. Abortive systoles.

The image of the curves in this stage is often a very irregular one, and it can only be analysed by taking into account the deviations of shape mentioned above. In Fig. 13 such an irregular image

Fig. 13.

of curves is represented. Now a systole of the ventricle falls out, now an enlarged systole of the ventricle occurs; after such an enlarged systole a little abortive one can follow, as I described above. Between these deformed systoles occur, on account of disturbances in the conductibility in the ventricle. In this way the play of the curves that was at first incomprehensible, becomes clearer. When the ventricle functions so irregularly, then the last stage is certainly reached which in literature is indicated as the toxical

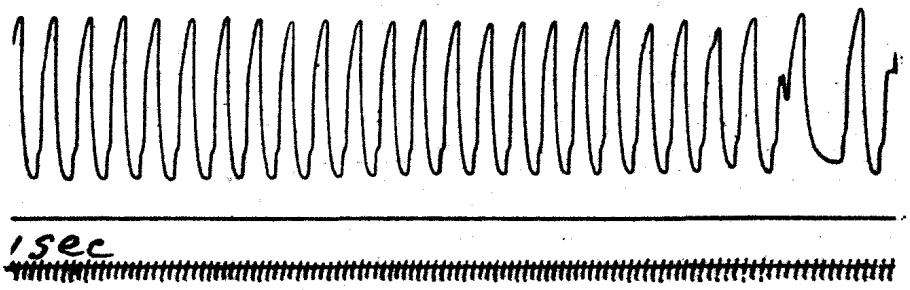


Fig. 14.

[1]) These Proceedings Vol. XVIII N°. 10 pag. 1588, 1916.

stage. It is remarkable that this toxical stage can promptly be reduced again to the normal rhythm in which every systole of the auricle is followed by a powerful systole of the ventricle.

In Fig. 14 we see a representation of the same frog's heart of Fig. 13, but now after the sinus venosus has two minutes previously been refrigerated during a short time. After this refrigeration the rhythm of the ventricle became quite normal again, so that every systole of the auricle was followed by a systole of the ventricle. After the refrigeration the sinus venosus assumes gradually again the temperature of its surroundings, by which the tempo of the pulsations of the heart is quickened again. The consequence of this is, that the toxical stage shows again irregular curves of the ventricle. On the diastolic line the last but one curve of the figure shows a second large elevation, which proves that at that moment the conductibility in the ventricle is considerably disturbed. This deformed curve is, as always is the case, followed by a prolonged pause and a succeeding enlarged systole. From this moment the former irregularities in the curves of the ventricle appear again. This experiment is very instructive. If we ask why through this simple intervention we could make the toxical stage return to the therapeutic one, the answer to this question can easily be found. The irregularities described above were brought about by the circumstance that the refractory stage of the ventricle or of part of the ventricle lasted longer than 1 sinus-period. Consequently the ventricle or part of it was at a given moment not able to react upon the "Erregung" that reached it from the auricle. The refrigeration of the sinus venosus prolongs the duration of the periods of the heart, so that the wrong proportion does not exist any longer and the normal rhythm is restored. This affords us a new indication that the irregularities we have described are caused by a wrong proportion between the duration of the refractory stage and the duration of the sinus-periods. This experiment teaches us likewise that in the pharmacy of the digitalisgroup a dose is then toxical, when the frequency of the heart is a definite one. At high frequencies the toxical dose is much smaller than at low frequencies. This holds likewise for veratrine.

3. *Third stage.* During the third stage the periods of Luciani occur. The auricles continue to pulsate during the pauses in the normal tempo, so that we have here to do with periods of the ventricle (consequently of the contracting extreme organ). The ascending-stairs in the beginning and the descending-stairs towards the end of a group

occur often, but not always (vide Fig. 15). As a transition to the stage of the periods of Luciani I found a periodical descent and

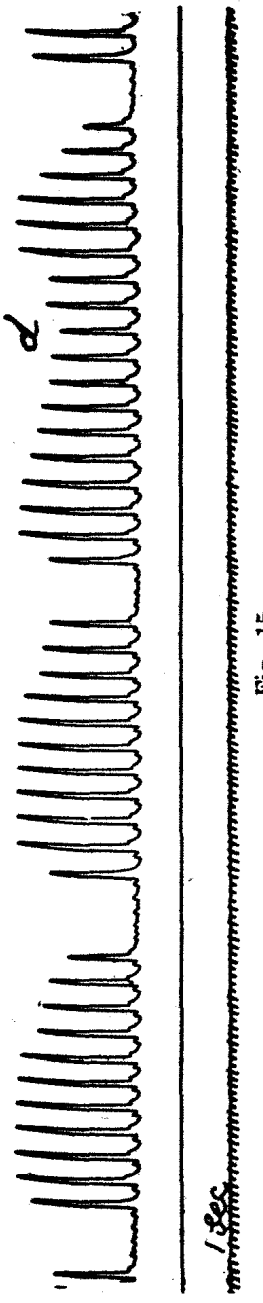


Fig. 15.

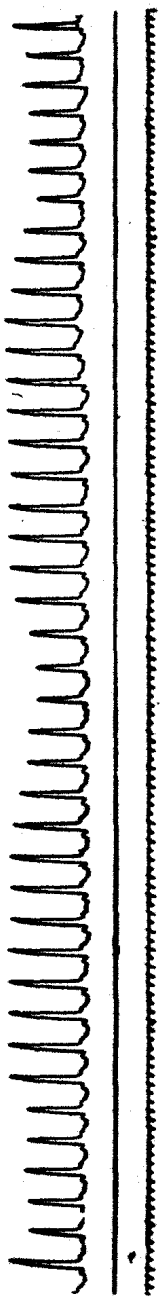


Fig. 16.

ascent of the curves of the ventricles as is represented in Fig. 16. These two figures originate from the same frog's heart; the curves of Fig. 16 were registered somewhat less than half an hour before these of Fig. 15. In Fig. 15 we see in the course of the 3rd group at *d* the curves of the ventricle descending and ascending again. It seems as if this group was dividing itself. This 3rd stage was treated

by me more elaborately in the Biological Section of the Society for promoting Physiology, Physic, and Surgery (Genootschap ter bevordering van Natuur-, Genees- en Heelkunde). Here I observe only that analogous observations were made by me after the poisoning of the frog's heart both with veratrine and antiarine.

The groups of Luciani were often followed by separate systoles of the ventricle (crisis of Luciani). There upon stagnation of the ventricle. It can likewise occur that the crisis does not set in at all.

LANGENDORFF and ÖHRWALL are of opinion that the variations of rhythm form the transition to the periods of Luciani. I can by no means share this view. It is true that in my method variations of rhythm proceed the periods of Luciani, but they do not occur in the latter part of the 2nd stage and, consequently, they cannot form the transition to the 3rd stage. They occur exactly *in the beginning* of the 2nd stage.

They are indeed variations between the 2nd and the 1st stage of poisoning [1]).

Amsterdam, 13 Nov. 1916.

Physiology. — "*On the Analogy between Potassium and Uranium when acting separately in contradistinction to their antagonism when acting simultaneously.*" By Prof. H. ZWAARDEMAKER.

(Communicated in the meeting of February 24, 1917.)

Physiologically there is some analogy between potassium- and uranium-salts. Both are strong poisons, the first for the heart, the second for the kidneys [2]). Again, in small doses they very largely aid the functions of these organs [3]). The automatically beating frog's heart, when fed artificially is a very suitable object to watch this useful action, as it is not fed along capillaries, but through lacunae penetrating everywhere from the cavity into the wall.

For artificial circulating fluids salt-solutions are used, so diluted that they possess the normal osmotic pressure and, moreover, contain next to each other 2 molecules of calcium chloride 1 or 2 molecules of

[1]) A more explicit paper follows in the Archives Neerlandaises de Physiology de l'homme et des animaux. Tome I. 3e livraison p. 502 (1917).

[2]) WOROSCHILSKY, Arb. a. d. pharmakol. Inst. in Dorpat. Bd, 5, 1890.

[3]) Moreover, in the concentration of $^1/_{1000}$n, uranium is conducive to alcoholic fermentation as well as to the growth of the tubercle-bacillus and the Bacillus pyocyaneus. (Vide BECQUEREL and others in C. R. t. 154 ff.).