Physiology. — "*On the transmission of stimula through the ventricle of frogs' hearts*". By Dr. S. DE BOER. (Communicated by Prof. VAN RIJNBERK).

(Communicated in the meeting of June 30, 1917).

The following facts were among others stated by me in the pharmacophysiological investigations I made into frogs' hearts, after I had poisoned them with veratrine or digitalis.

1. The duration of the refractory stage of the ventricle-muscle increases after the administration of each of the two poisons, and so does likewise the *a-v*-interval, at last the contractility of the ventricle-muscle decreases.

2. As soon as the relative duration of the refractory-stage $\left(\frac{\text{duration of the total refract. stage}}{\text{duration of a sinusperiod}}\right)$ surpasses the value 1, suddenly or gradually the normal ventricle-rhythm changes into the halved one.

a. The sudden halving of the ventricle-rhythm comes about in the following manner:

The duration of the refractory-stage of the ventricle has increased during the normal rhythm of the ventricle for this reason that the ventricle-muscle was not yet entirely restored at the beginning of every ventricle-systole. What was still wanting to this restoration, was called by me the *residue refractory stage.*

The *periodical refractory-stage* was added to it by every systole, so that the total refractory-stage consists of two components. If now the relative duration of the refractory-stage has become longer than 1, the next following ventricle-systole falls away, and a protracted ventricle-pause is the consequence. This protracted pause influences the two components in an opposite sense.

The ventricle-muscle restores itself better, so that the residue-refractory-stage decreases. But after a protracted pause the next following systole of the ventricle is considerably enlarged, consequently the duration of the periodical refractory-stage of the ventricle increases. If now this increase of the duration of the periodical refractory-stage surpasses the decrease of the residue-refractory stage, then suddenly halving of the ventricle-rhythm sets in.

b. The gradual transition to the halved ventricle-rhythm however

takes place, when the decrease of the residue-refractionary-stage surpasses the increase of the periodical refractionary-stage. For, if this takes place, the normal ventricle-rhythm continues after a protracted pause, till by accumulation the duration of the residue refractory-stage causes again the falling away of a ventricle-systole, and the normal ventricle-rhythm is resumed again. So groups of ventricle-systoles come into existence, which become gradually smaller and smaller, till in the end the halved ventricle-rhythm is reached in this way.

3. Spontaneous alternations between the halved ventricle-rhythm and the normal one occur frequently. The cause of these alternations lies in the fact that during the halved ventricle-rhythm the katabolic index of the ventricle $\left(\frac{\text{duration of the refract.stage of the ventricle}}{\text{duration of a ventricle-period}}\right)$ decreases again by restoration, till it has become less than $^1/_2$. Then the normal ventricle-rhythm sets in again. In this twice as rapid ventricle-rhythm [1]) the katabolic index of the ventricle increases again, and consequently the halved rhythm of the ventricle sets in again. So these alternations can repeat themselves again several times.

4. By extra stimulation of the ventricle the halved ventricle-rhythm can artificially be converted into the normal twice as rapid rhythm by the addition of one little ventricle-systole. This proves, that during the halved rhythm of the ventricle the sinus-impulses that are not answered by the ventricle, did really reach this part of the heart, but rebounded on the not yet irritable ventricle-muscle.

The normal ventricle-rhythm can likewise be converted into the halved one by extra-stimulation. The enlarged post-compensatory-systole fixed then the ventricle in the halved rhythm.

I attributed these and many other results, not mentioned here, to the fact, that an important factor of the action of the heart, viz the refractory stage had been modified under the influence of the employed poisons. Its duration increased by veratrine and by digitalis. These poisons had no further possible mysterious actions for the results, mentioned above.

The following observations made with regard to not poisoned frogs' hearts afforded an unmistakable affirmation of this fact. *The before mentioned sudden and gradual transition into the halved ventricle-rhythm occurs likewise in the not poisoned frog's heart, the spontaneous alternations between the halved rhythm of the ventricle and the normal one can also be stated.*

[1]) During the normal ventricle-rhythm the katabolic index of the ventricle is equal to the relative duration of the refractory stage.

In fig. 1 [1]) we give a reproduction of the suspension-curves and the electrograms of a frog's heart (rana esculenta). More than an hour after the suspension this heart shows constantly repeated

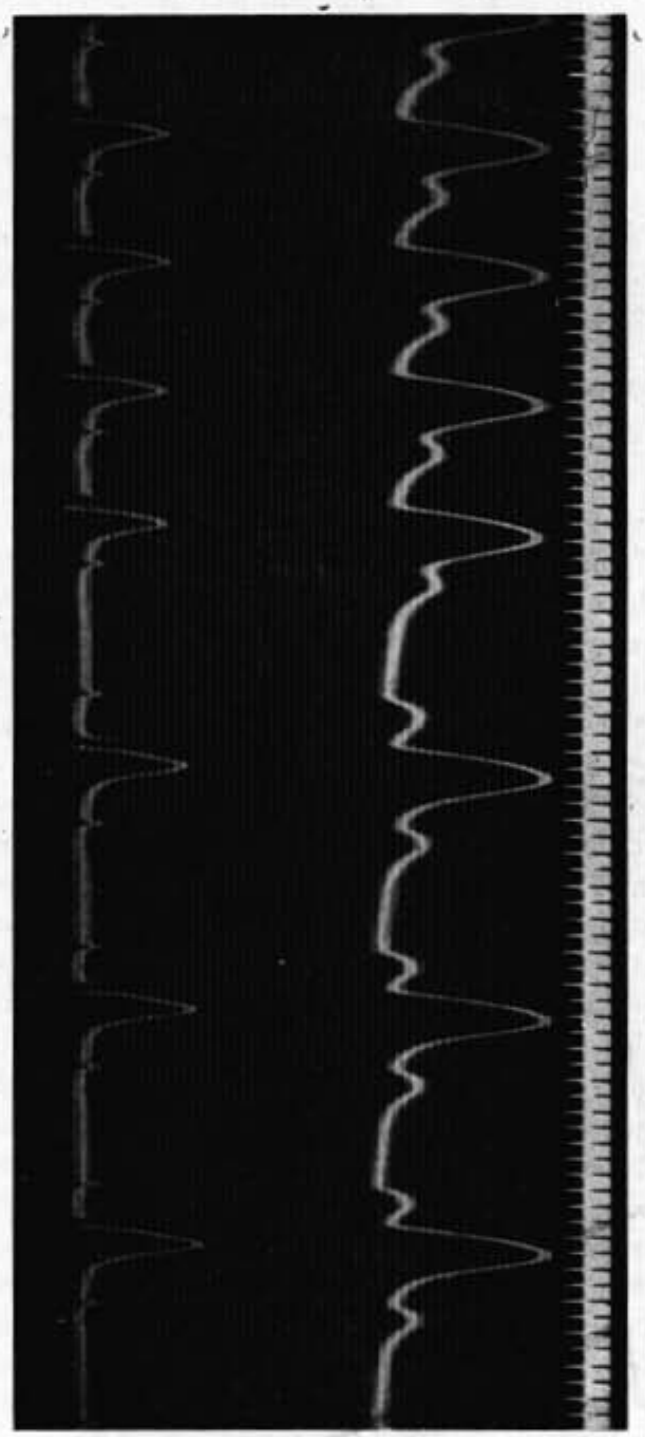

Fig. 1.

[1]) Constantly 1 electrode was placed on the auricle — and 1 on the ventricle-point in the following reproductions.

alternations between the normal ventricle-rhythm and the halved one. I succeeded in photographing such a spontaneous alternation under simultaneous registration of the action-currents.

This reproduction shows a great number of important details, and affords a formal confirmation, likewise for not-poisoned frogs' hearts, of the theoretical explanations communicated by me in former essays. In the figure we see suddenly appear the halved ventricle-rhythm after 4 normal ventricle-systoles. Three of these are still registered.

I intend more explicitly to explain here the following details, which, in my opinion, are of interest for my subject.

1. As I indicated in my former investigations the a-v-interval increases during the normal ventricle-rhythm till the halving of the ventricle-rhythm sets in. Afterwards the duration of the a-v-interval decreases. The suspension-curves of this figure show a much shorter a-v-interval after the halving than before it. But the electrograms indicate these differences much sharper. The P-R-interval increases still during the last 4 systoles. The first curve of the halved ventricle-rhythm shows a much shorter P-R-interval of the normal ventricle-rhythm. The restoration of the ventricle-muscle in the halved rhythm is even distinctly to be seen in these 3 first curves of the halved ventricle-rhythm. The P-R-interval of the 2nd systole is shorter than that of the first, and that of the 3rd still shorter than that of the 2nd.

We must attribute the shortening of the P-R-interval after the halving to a shortening of the electric latent stage, as all sinus-impulses reach the ventricle along the connection-systems (Bundle of His), and consequently the time of conducting along these has not in the least changed. It appears that this shortening still proceeds from the moment of the first ventricle-systole of the halved rhythm.

2. The duration of the R-oscillation is after the halving shorter than before it. This duration is now also again shorter during the 2nd systole than during the first, and at the 3rd systole shorter than at the 2nd.

In the halved ventricle-rhythm the conductivity through the ventricle is consequently better than in the normal twice as rapid rhythm of the ventricle. From the first systole of the halved ventricle-rhythm the conductivity still improves from systole to systole.

The P-R-interval and the duration of the R-oscillation consequently sustain alterations in exactly the same sense. We must attribute both these alterations to the changed metabolic condition of the ventricle-muscle (katabolic index). This metabolic condition deteriorates in the normal ventricle-rhythm. If now the rhythm of the

ventricle suddenly halves, the metabolic condition of the ventricle-muscle suddenly improves much, but also in the halved ventricle-rhythm this improvement increases from systole to systole.

This reproduction which for the present moment will remain most likely exceptional among my material, afforded me an irrefutable confirmation of the theories I explained before. For the present I

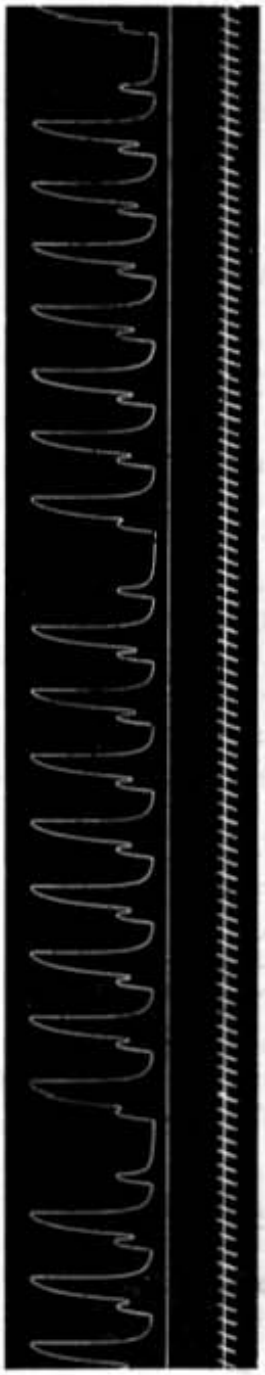

Fig. 2.

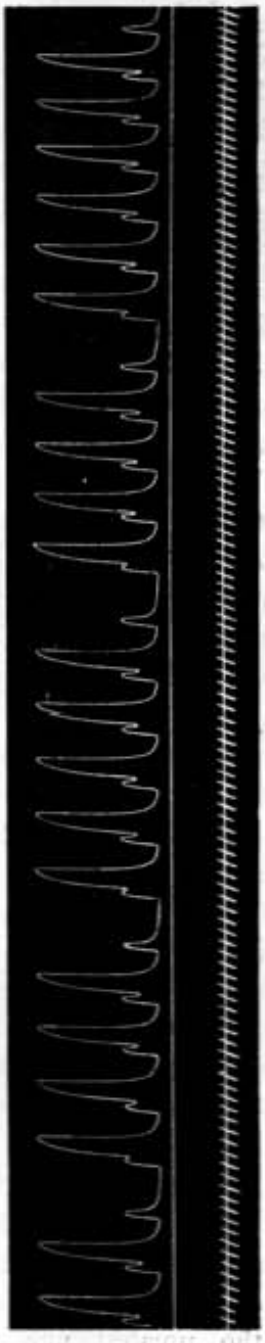

Fig. 3.

shall most likely be compelled in my further investigations to restrict myself to artificial transitions of poisoned frogs' hearts, and, when doing so, I shall at the same time register the action-currents.

I am likewise in possession of beautiful examples of the slow transition to the halved rhythm of unpoisoned frogs' hearts. One example of these is reproduced in the figures 2, 3, 4, and 5.

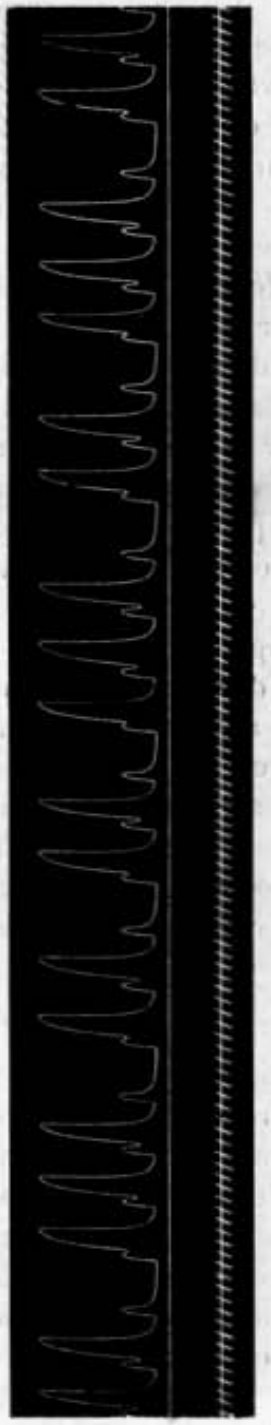

Fig. 4.

Fig. 5.

The heart of a rana temporaria was suspended and soon showed group-formation, because constantly 1 systole of the ventricle fell away. The groups grow gradually smaller, till groups of 2 and 3 systoles (fig. 4) form the last transition to the halved ventricle-rhythm. (fig. 5). We see during the groups the duration of the *a—v* interval increasing splendidly; again and again the ventricle-systole sets in later in the auricle-diastole, till one ventricle-systole falls away. After this the interval is shortened again, to be protracted again in the same way during the following group. The ventricle-systole of each first curve of the group commences in the figures 2, 3 and 4 close to the top of the auricle-curve. The ventricle systole of each last curve begins at about the middle of the diastolic line of the auricle-curves. This is the case with the large groups, but also with the little ones (bigeminus groups). Consequently in the beginning more systoles of the ventricle are required than later to protract the *a—v*-interval as much. The deterioration of the metabolic condition of the ventricle-muscle is announced here by the formation of smaller groups. It is likewise clear, that during the groups the metabolic condition of the ventricle-muscle deteriorates, and improves again after a protracted pause. In my opinion we must here also attribute the protraction of the *a—v*-interval again to a protraction of the latent stage of the ventricle-muscle.

It is the active contracting terminal organ, the ventricle-muscle, the refractory stage of which increases during the groups and so does at the same time likewise the latent stage. The increase of the refractory-stage is here likewise caused by the increase of the duration of the residue-refractory-stage by accumulation. During the protracted pause after a group the decrease of the residue-refractory-stage surpasses the increase of the periodical refractory-stage. In this way the constantly decreasing groups come into existence, which ends in the halved ventricle-rhythm.

The conductivity through the ventricle was examined by me still in another way. In a former communication it was already stated, that the T-oscillation had altered in a negative sense after extra-stimulation of the ventricle-basis or of the auricle. A positive T of the normal ventricle-systole decreased during the extra-systole which was excited in this way, a negative T increased. In some cases a positive T became negative. The T oscillation had changed in a positive sense after extra-stimulation of the ventricle-point. A negative T decreased, a positive one increased [1].

[1]) Zeitschrift für Biologie. Bd 65, Seite 428.

These modifications of the T-oscillations were now examined by me more carefully, and it appeared to me, that the conductivity of the ventricle plays here an important part. *I stated in this examination that the T-oscillation varies the more in a negative sense, after*

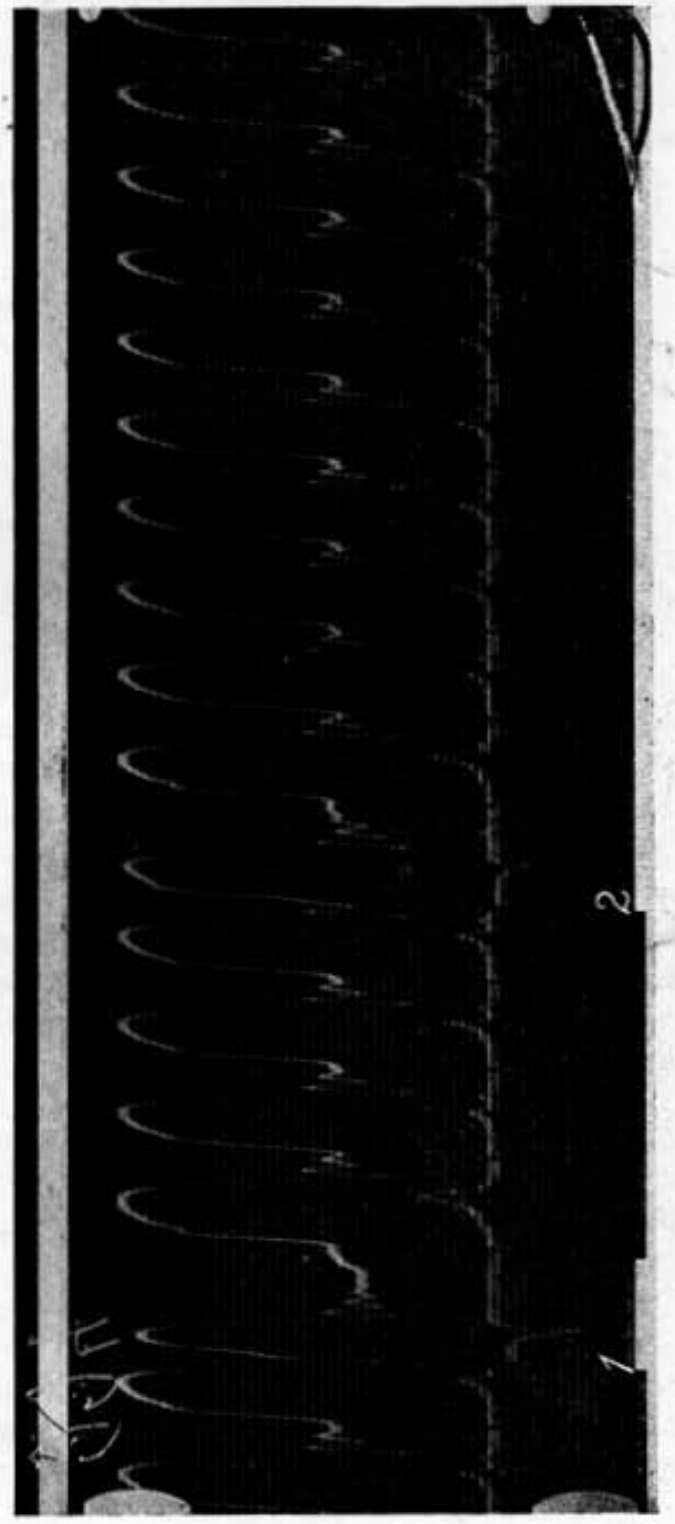

Fig. 6.

extra-stimulation of the ventricle-muscle or of the auricle, in proportion as the conductivity of the ventricle is worse at the moment, when the extra stimulation or the "Erregung" conducted after the provoked auricle-extra-systole reaches the ventricle at an earlier epoch of the ventricle-period.

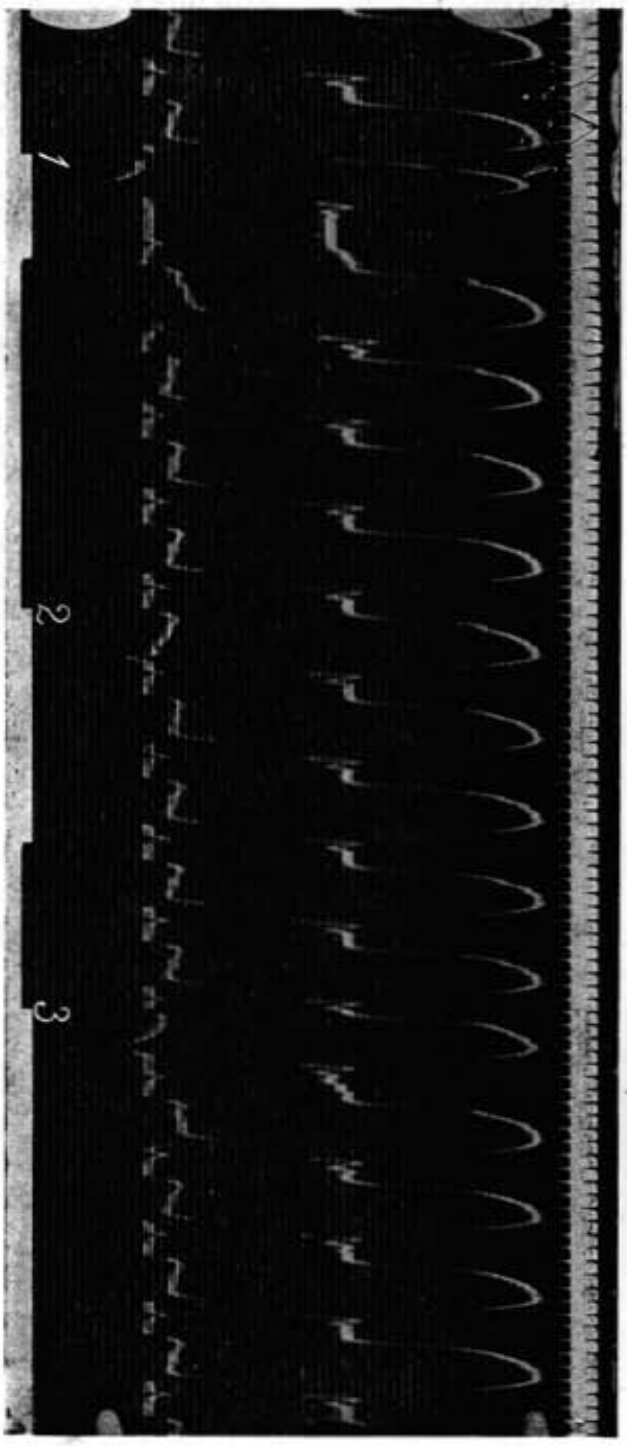

FIG. 7.

The positive T-oscillation of the normal systoles during an extra-systole can even produce a negative T, if at an early epoch of the ventricle-period the ventricle is excited to an extra-contraction, and a decreased positive T, if at a later epoch of the ventricle period the ventricle is excited to an extra-contraction.

A few examples may explain the above more accurately.[1]) In the figures 6 and 7 extra-stimula were applied to the ventricle-basis at the upward oscillations of the signal. In Fig. 6 at 1 an extra-stimulus is applied to the ventricle-basis immediately after the completion of the preceding T-oscillation. The T-oscillation of the extra-systole which is positive at the normal ventricle-systole, becomes now decidedly negative. At 2 a following extra-stimulus hits the ventricle-basis at a much later epoch; consequently the negative T-oscillation is now much smaller. Here I already fix the attention to the fact that the enlargement of the positive T-oscillation is so much the more important during the postcompensatory-systole, in proportion as the preceding extra-systole has been brought about at an earlier epoch of the ventricle-period.

In fig. 7 an extra-stimulus hits the ventricle-basis at 1 soon after the completion of the preceding T-oscillation. This causes a great negative T in the electrogram of the ventricle-extra-systole. At 3 the extra-stimulus hits the ventricle at a later epoch, this makes the T-oscillation smaller, at 2 the extra-stimulus comes still later, an extremely little negative T-oscillation is the consequence.

It is beautifully brought out here, that the enlargement of the positive T-oscillations of the postcompensatory systoles is so much the more important, in proportion as the extra-stimulus has hit the ventricle-basis at an earlier epoch of the ventricle-period.

The extra-stimulus was applied to the auricle in the figures 8 and 9, which proceed from the same frog's heart. At about the same epoch of the ventricle-period the ventricle-systoles set in that are brought about after auricle-extra-systoles by the conducted "Erregung" after the extra-stimula applied at 1 and 4. The T is negative and of the same dimension at both the ventricle-systoles brought about in this way. The ventricle-systole sets in at a much later epoch of the ventricle-periods after the extra-stimulus applied to the auricle at 2. The T-oscillation remains now positive, though distinctly reduced.

At 3 an extra-systole of the ventricle is brought about through current-loops directly by the stimulus.

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[1]) In the following figures extra-stimula were only applied at the upward oscillation of the signal.

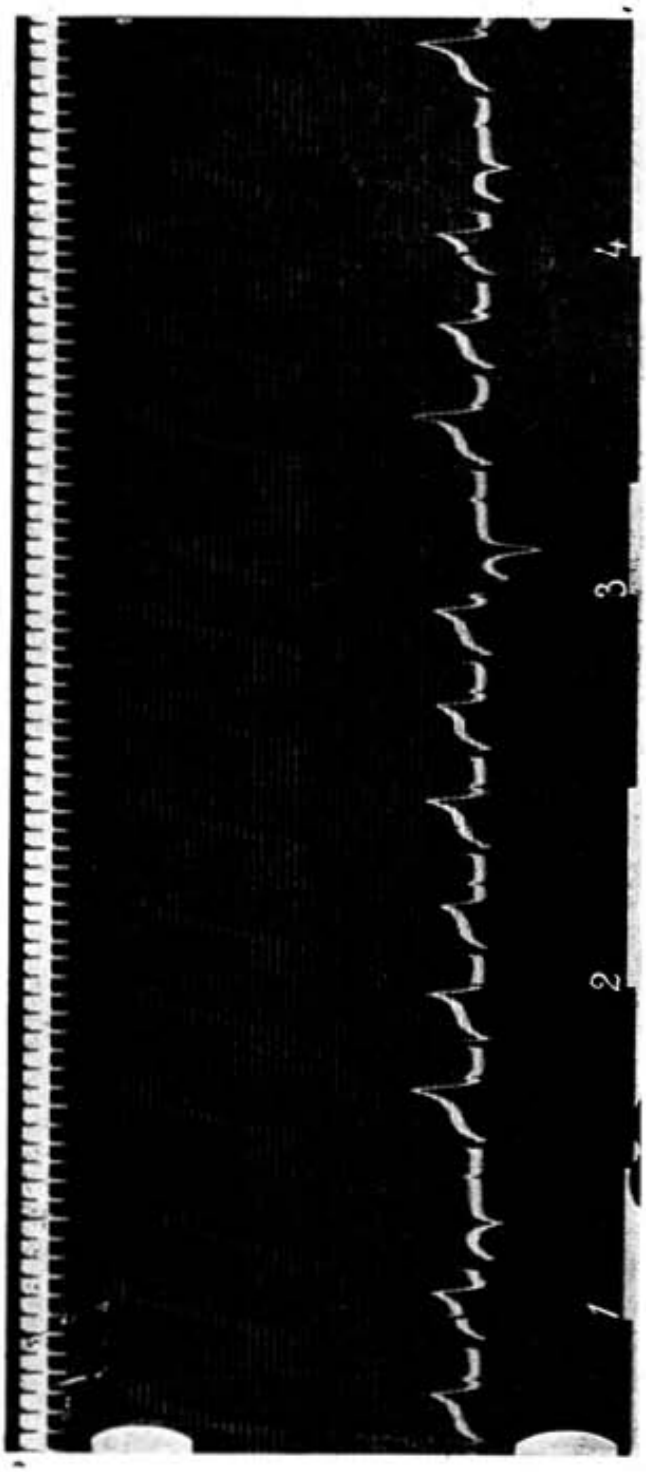

Fig. 8.

At 5 and 7 the ventricle-systoles caused in the same way set in at a much earlier epoch of the ventricle-period than at 1 and 4. In conformity herewith both the negative T-oscillations are now also much greater. The ventricle-systoles that are brought about

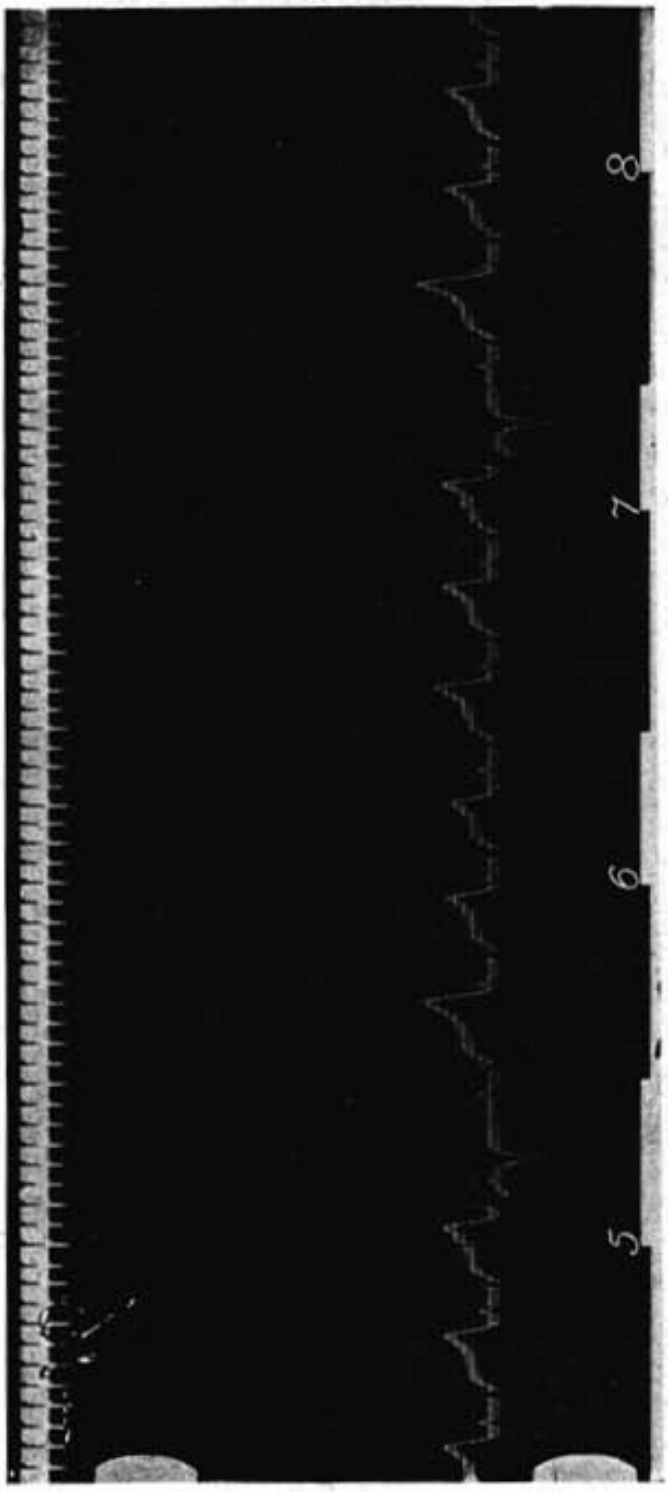

Fig. 9.

after 5 and 7 teach us how exactly the dimension of the negative T-oscillations is determined by the epoch of the ventricle-period at which the ventricle systoles are brought about. After the extra-stimulation of the auricle at 5 the string is a little longer in the

position of rest, after the completion of the T-oscillation of the ventricle, before the R-oscillation of the anticipated ventricle-systole begins, than after the extra-stimulation at 7. The difference is little but it can distinctly be observed. Entirely in conformity herewith the negative T is after the extra-stimulation at 5 smaller than after the extra-stimulation at 7. At 6 the anticipated ventricle-systole begins, after the extra-stimulation of the auricle at a much later moment of the ventricle-period. The T-oscillation remains now positive, but is somewhat reduced. The extra-stimulation at 8 has evidently hit the auricle at the same moment, as it was reached by the sinus-impulsion.

In these representations the enlargement of the positive T-oscillation of the post-compensatory systoles is also the greater, in proportion as the extra-systole of the ventricle sets in more anticipated.

If now we try to answer the question, why the T-oscillations of the ventricle-electrograms change the more in a negative sense after extra-stimulation of the ventricle-basis and the auricle, in proportion as the extra-ventricle-systole begins earlier in the ventricle-period, then we must look for the cause of this phenomenon in the conductivity of the ventricle. At an earlier epoch of the ventricle-period this conduction is slower than at a later period

This is the cause that the negativity of the point at an extra-systole, which has been brought about at an earlier epoch of the ventricle-period, begins later than at an extra-systole that has been brought about at a later epoch. Consequently the point-negativity domineers the more in the latter part of the ventricle-electrograms, in proportion as the extra-systole has been brought about at an earlier epoch of the ventricle-period. The earlier the extra-systole is brought about in the ventricle-period, the more the T-oscillation changes in a negative sense. It is likewise moreover of importance in this respect that the contractility of the basis at an early epoch of the ventricle-period is still trifling; when from there the contraction-wave reaches the point in a slow tempo, its contractility has become more intensive. But this factor can be reduced again to a slackened conductivity at an early epoch of the ventricle-period. This theoretical explanation corresponds so perfectly with the experimental results, that I can discretionally produce extra-systoles with reduced positive T-oscillations and with negative T-oscillations.

I wish to fix here the attention to one point that is distinctly demonstrated in the figures 8 and 9, I pointed out in my former communication already, that after extra-stimulation of the auricle and of the basis ventriculi the T-oscillations of the ventricle-

systoles were modified in an equal sense. This appears most distinctly from the figures 8 and 9, in which at about the same epoch of the ventricle-period, at 3 by extra-stimulation of the basis ventriculi (by current-loops), and at 5 and 7 after extra-

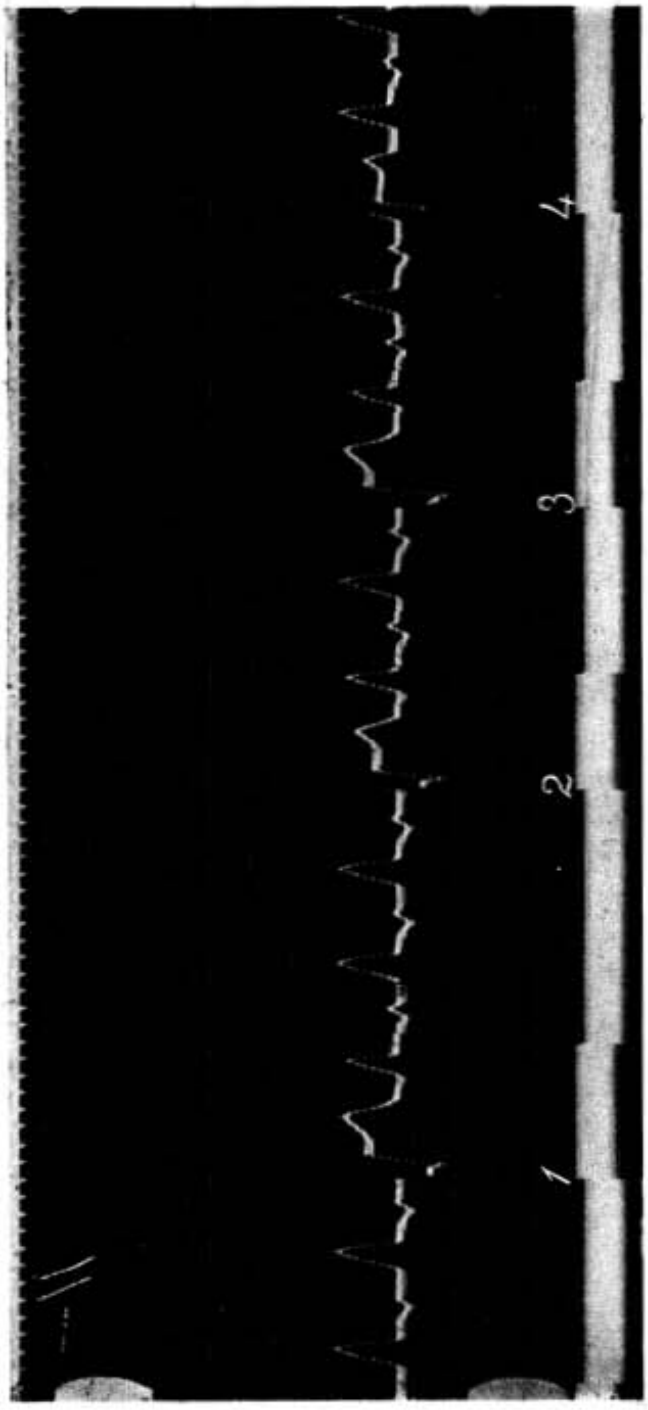

Fig. 10.

stimulation of the auricle, an extra-ventricle-systole is brought about. We see now the T-oscillation after extra-stimulation of the basis ventriculi about as large as after extra-stimulation of the auricle. The anticipated ventricle-systole is brought about in the latter case by the "Erregung" that reaches the ventricle along the usual connection-systems. The epoch of the ventricle at which the anticipated ventricle-systole begins, and not the place where the stimulus attacks, determines the extent of the T-oscillations. It is obvious that this does not hold, when an extra-stimulation hits the point. But here the T-oscillation of the ventricle-systole varies the more intensively in a positive sense, in proportion as the extra-stimulus reaches the ventricle at an earlier epoch of the ventricle-period. This is distinctly to be seen in Fig. 10. At 1 and 3 the extra-stimulation reaches the ventricle-point at an early epoch of the ventricle-period. Now very large positive T-oscillations set in. At 2 the extra-stimulation hits the ventricle-point at a later epoch. Consequently the positive T is now smaller. If at 4 the ventricle-point is hit by the extra-stimulation at a still later epoch, the positive T is again still considerably smaller. At 4 the basis-negativity had already begun, when the extra-stimulation set in, and brought the string back to and beyond the O-position. It appears consequently that the ventricle-point is irritable in the ascending line of the R-oscillation.

The basis-negativity is consequently so much the more intensive in the ventricle-electrograms of the extra-systoles after extra-stimulation at the end of these electrograms, in proportion as the extra-stimulation hits the ventricle-point at an earlier epoch of the ventricle-period.