THE INFLUENCE OF VERATRIN POISONING ON THE ELECTROGRAM OF THE FROGS' HEARTS.

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The researches made by Seemann(1) show that in veratrin poisoning there is a general heightening of the tonus of the heart muscle, which is strongest at the apex. Further, during the poisoning there are repeated inverse electrograms of the ventricle, in which the stimulation is conducted from the apex to the base. After the apex had been cut off, Seemann observed that after immersion in a strongly diluted veratrin solution, it was subject to spontaneous pulsations. Thus it may be considered as certain that even in the apex of the heart the stimulation which causes systole may originate. Seemann also found an increase of the after-variation (Nachschwankung). By this he means the part of the ventricle electrogram following the *R*-top. At the same time he found the *R*-top heightened. During the staircase phenomenon, Seemann found that the *R*-top kept the same level, whilst the *T*-top mostly increased. From these experiments he concludes that in the ventricle electrogram the *R*-top is the expression of the conduction of the stimulation and to be compared with the action current of a skeletal muscle, whilst the *T*-top is a phenomenon accompanying the contraction.

Veen(2) found after veratrin poisoning an increase of both the *T*-top and the *R*-top. After cooling he found an increase of the *T*-top, after warming, a decrease.

Last year I made extensive researches with regard to the changes in the rhythm and the conductivity and irritability of the heart muscle and the conductivity of the connecting systems of the heart partitions after veratrin poisoning(3). On the results of these experiments, which opened up to me various new points of view, I based the study of the electric potential differences in the heart muscle under these conditions of poisoning. Thereby it was rendered easy to recognise quickly the various stages of the poisoning and the better to overcome the various factors, which may influence the electrogram during these stages.

Method. The heart was exposed with as little loss of blood as possible, the pericardium was severed and the fremulum cut through. The heart thus isolated was suspended at the apex to a lever, the shadow of which was transferred to the sensitive plate through the fissure of the fall-apparatus. The leading off was effected by wire electrodes from the apex and the auricle. The time was recorded in $\frac{1}{5}$ second. Before the poisoning one or two records were made, then I injected five to ten drops of 1 % veratrin acetate solution into the abdomen, without moistening the heart. Records were made in the course of the various stages of the poisoning. It is a well-known fact—which I can fully confirm—that after the veratrin poisoning the *a–v* interval increases in length and the irritability of the ventricular musculature decreases. In regard to changes in the conduction of the stimulation in the ventricle itself after veratrin poisoning, however,

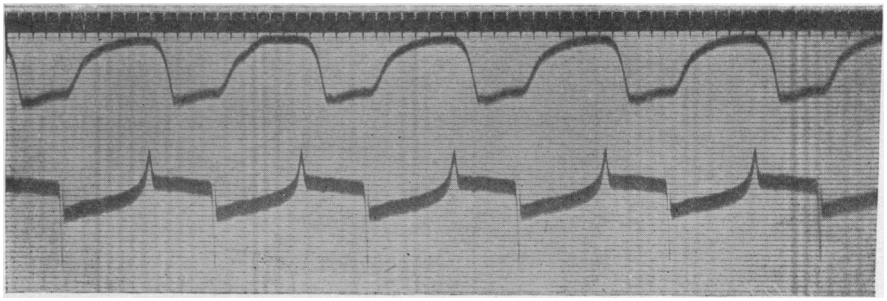

Fig. 1. (This and other figures $\times \frac{2}{3}$.)

there is hardly any certainty. Especially with a view to this fact have these experiments been made.

I give here a short account of typical experiments.

A frog's heart *in situ* was suspended with intact circulation. With leading off from apex to auricle I made a record at 11.25 (Fig. 1). Tension of string $1mV$ $1\frac{1}{2}$ mm., time $\frac{1}{5}$ second, 30,000 ohms resistance were intercalated. If the base of the ventricle is negative, the string makes an excursion away from the line indicating the time; if not stated otherwise this is always the case in further records. In this experiment the *R*-top is positive, the *T*-top negative. At 11.30 five drops 1 % veratrin is injected into the abdomen and at 11.42 I make another record under the same conditions of leading off, tension of string and resistance (Fig. 2). [In the following records the manner of leading off, the tension of the string and the intercalated resistance, if not

stated otherwise, are always the same.] The rhythm of the heart has now slowed down, the *a–v* interval has lengthened (the *P*-top is not to be seen). The systoles have decreased in size[1]. The intervals between the ventricular mechanograms have strongly increased in length, whilst those between the ventricular electrograms have decreased. The cause of this lies in the fact that the end of the *T*-top before the poisoning coincides with the beginning and after the poisoning with the end of the diastole, and that after the poisoning the interval between the beginning of *R* and the beginning of the ventricular systole has considerably gained in length (this interval I shall henceforth call the *R–V* interval). The latent stage for the ventricle has thus strongly increased, but at the same time the electric variations are observed, until the end of the systole. In previous experiments I always found after the poisoning an increase of the refractory stage; even by the

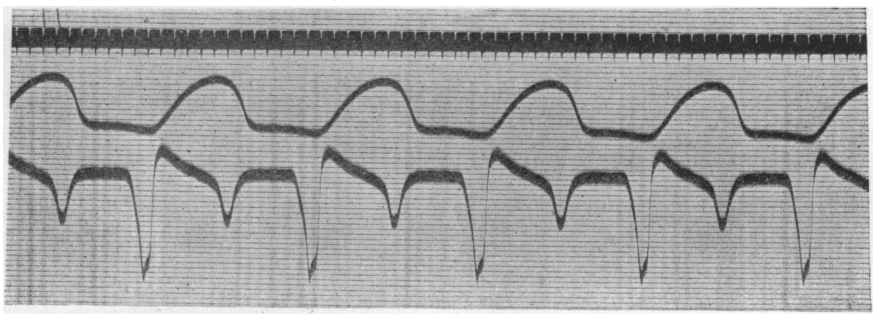

Fig. 2.

strongest stimuli I did not succeed in exciting an extrasystole during the diastole. We see in this record that the increase of the refractory stage is coupled with an increase in duration of the electrogram. Thus in the case of the non-poisoned heart the refractory period extends to the beginning of the diastole. These two experiments demonstrate clearly the coincidence of the refractory period and the duration of the electric phenomena. This rule, however, does not hold good in all respects. In hearts poisoned by veratrin I found that in certain stages of the poisoning the refractory period repeatedly extended far into the pause, and in no case did the electrograms last longer than the end of

[1] In my previous experiments, which will appear in the *Arch. Néerland. d. Sci. ex. et nat.*, I stated that only after the poisoning the systoles increased in length, decreasing again before the halving. Thus this experiment was made in the stage in which the size of the systole had again decreased.

the diastole; the reason of this is that the heart muscle in these cases cannot recuperate sufficiently, and thus the refractory period depends not only on the one preceding systole, but on all the preceding systoles which have contributed their share. Consequently the heart is not in metabolic balance.

Thus I should suggest the following general rule: So long as the heart functions in metabolic balance, the duration of the refractory period coincides with the duration of the action current; if, on the contrary, this balance has been disturbed, the duration of the refractory period is longer. Several physiologists have already searched for a relation between the duration of the electrograms and the duration of the refractory period.

The duration and the height of the *R*-top have strongly increased[1], the *R*-top has split, the *T* has become positive, whilst the connecting line between the *R* and the *T* has sunk.

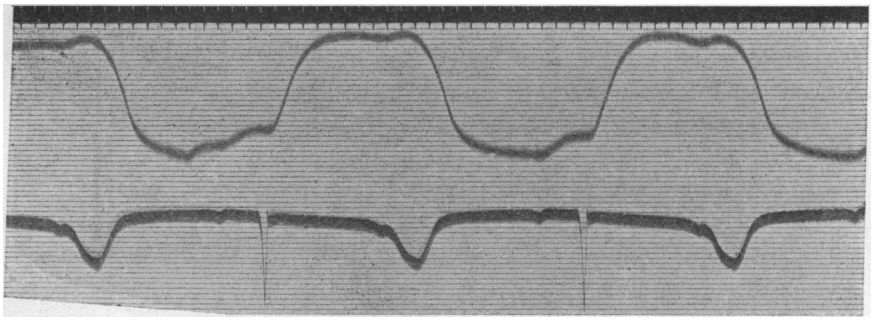

Fig. 3.

At 12.50 I made the record shown in Fig. 3. The rhythm of the ventricle has just before been halved, whilst there has been no change in that of the auricle. Every second auricle, to which the ventricle does not respond, coincides with the end of the systolic plateau of the ventricular curve. The height and the duration of the systoles have strongly increased. This increase is in the first place a result of the slower rhythm, but the veratrin poisoning also contributed towards it. The auricular systoles, however, have also become more vigorous, which probably is to be attributed to the increased influx of blood. The electrogram has undergone a considerable change. In the first

[1] After veratrin poisoning the blood-filling of the ventricle always decreases; therefore the increase of the height of the *R*-top is probably wholly or partially a consequence of this phenomenon.

place the P has been increased, but to this I should not like to attach too much value, for veratrin poisoning always causes a strong decrease in the influx of blood to the heart. And now it is known from one of my previous experiments how much this increases the excursions [cp. (4)]. True, the influx of blood increases again by the halving of the rhythm, but this only as compared with the stage of poisoning before the halving. The P–R interval has strongly decreased; it is even shorter than before the poisoning. This shows that even in the case of a poisoned heart, the interval between auricle and ventricle is shortened after the ventricular rhythm has been halved. Whilst veratrin poisoning increases this interval, nevertheless the interval between auricle and ventricle is still shorter than before the poisoning. The cause of this does not lie in a better conduction along the connecting systems, but in the fact that the ventricular musculature responds more promptly to the stimulation. For the stimulation after the two auricular systoles, which takes place during one ventricular systole, is, indeed, conducted towards the ventricle along the connecting systems. To every second auricular systole the ventricle does not respond, because at that time it is refractory. There is, therefore, no reason why this *conduction* after the halving of the ventricular rhythm should at once improve. That this is so I can prove by experimental data, which I shall afterwards explain more fully by curves. The R–V interval has again become shorter and the electrogram of the ventricle also has considerably changed. The height of the R-excursion shows a considerable decrease (probably by the increase in the influx of blood); it is of greater importance, however, that the duration of the R has again been greatly reduced. In my previous publication on the extrasystole (4) I demonstrated that the duration of the R gives a measure for the conduction of the stimulation in the heart muscle. This is again proved in this instance. Before the ventricular halving, the conduction of the stimulation in the heart muscle slowed down, and the duration of the R has strongly increased. After the halving, the conduction of the stimulation in the ventricle has improved and the duration of the R has been correspondingly shortened. After longer pauses—and this proved true also in my researches for the extrasystole after the longer compensatory pause—the conductivity of the ventricular musculature has improved. The T-excursion has broadened: in the beginning of the T we see the second P. At a short distance from the R we find a fairly rapid small excursion, which is probably to be attributed to the bulbus. The duration of the entire ventricular

electrogram has strongly increased. This increase is entirely caused by the increase of the part following the *R*-excursion. The *T*-excursion again ends at an earlier period of the diastole than in the preceding experiment. This shows that the refractory period again ends earlier in the diastole. And I have invariably found that the irritability of the heart muscle in the diastole increases again after the halving (3, 5).

At 1.25 I made another record. The size of the systole has again decreased, the rhythm has slowed down. The *P–R* interval has again increased in length and the *R–V* interval also. The duration of the *R* has increased, the top has again split. The increase in duration of the *P–R* interval and the broadening of the *R*, point out that the conductivity of the connecting systems and of the ventricular musculature has suffered still further from the progress of the poisoning process.

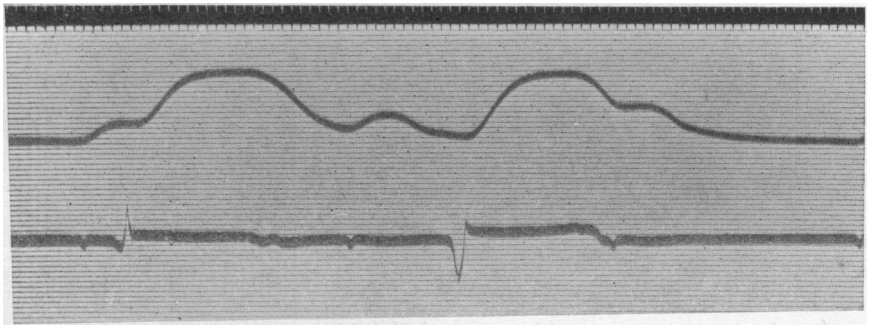

Fig. 4.

At 2.15 there is another record. The frequency of the systoles has again decreased, the *a–v* (*P–R*) interval has increased. If now we examine the heart, we note that with every other pulsation the ventricular contraction alternately begins near the apex and near the base. Correspondingly we also see the *R*-excursion negatively and positively directed. The systoles of the apex type are larger than those of the base type. The experiment of 2.40 (with a slower movement of the plate) is represented by Fig. 4. Here we see as a transition to another halving of the ventricular rhythm every third ventricular systole eliminated, so that consequently the heart is gradually getting to pulsate in bigeminous groups. Each bigeminous group is composed of one systole of the base type and one of the apex type, and just as in the previous experiment that of the base type is the narrower. The systole of the apex type which is preceded by a longer pause, has a *P–R* interval

smaller than in the previous experiment; in that of the base type the *P–R* interval has much increased. Thus, here we see again a better conduction in the connecting systems (and an improved irritability of the ventricular muscle to the arriving excitation) after the longer pause, whilst after the shorter pause this conduction is less efficient. I also observed the same phenomenon in the case of the extrasystoles originated in the auricle and in the post-compensatory systole. In the former the conduction of the connecting bundles was slower (longer *P–R* interval), in the latter it was much improved (shorter *P–R* interval). When I speak of a more or less efficient conduction in the connecting systems, I always include the time necessary for the excitation, coming on from the auricle, to make itself felt in the ventricle. This latter space of time depends on the irritability of the ventricle: we always judge the conduction according to the duration of the *a–v* or *P–R*

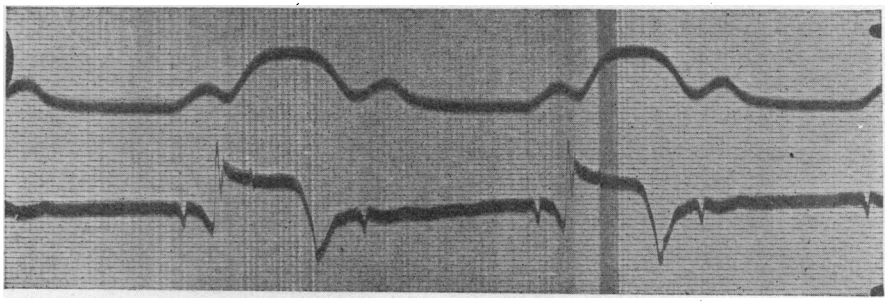

Fig. 5.

interval and this includes two factors, viz. the time of conduction along the connecting systems and the time of latent stimulation of the ventricular muscle.

In the next record, at 3 o'clock, the halving of the ventricular rhythm has again been completed. The auricular rhythm, which was halved after 1.25, is still in the first halved stage, so that now there is again one ventricular systole to every two auricular systoles. The ventricular pulsations are now all of the apex type. The *P–R* interval has again been shortened, as has the *R–V* interval; the breadth of the *R*-branch has again decreased.

At 4.10, the heart is still pulsating in the same rhythm. A record with a slower movement of the plate is taken (Fig. 5). The ventricular electrogram has changed again; whilst the connecting line between the *R* and the *T* has risen, a large positive *T* has taken existence. These

electrograms are fairly complete. We see here before the *P*-top a small positive top, evidently the *Si*-top. The auricular electrogram (for the odd auricular systoles) is composed of a positive *P*, thereupon a slow positive excursion, followed by a small top in a negative direction. Moreover, these electrograms show a plainly visible bulbous branch, as was the case in nearly all previous records.

We have seen that in this frog's heart during the veratrin poisoning the conduction of the stimulation between the auricle and the ventricle slowed down (viz. that the *P–R* interval lengthened); we also observed a slowing down of the conduction of the stimulation in the ventricular musculature (broadening of the *R*-excursion) and an increase in the latent stage of the ventricular muscle (*R–V* interval). When, thereafter, by the lengthening of the refractory period and of the *a–v* interval the ventricular rhythm is gradually halved, both the conduction between auricle and ventricle and within the ventricular musculature and the *R–V* interval improve. The extent of these three values in this rhythm also increases by the advancing poisoning, until finally a second halving of the rhythm of the ventricle occurs. A transition to this second halving is constituted by bigeminous groups. Each bigeminous group is composed of one systole of the apex type and one of the base type. The *P–R* interval after the longer pause has been shortened, after the shorter pause it has been lengthened. Thereupon there is another halving of the ventricular rhythm. The systoles are now of the apex type, the conduction in the connecting systems has again improved, which is also the case in the ventricular musculature (narrow *R*-excursion) and the *R–V* interval has been shortened. Finally I give a complete electrogram, containing all possible excursions. The oscillations in the conduction of the stimulation in the connecting systems and in the musculature of the ventricle, are the result of two factors, viz. (1) the poisoning which impairs the conduction, and (2) the process of rhythm-halving, which leads to an improvement of the conduction in the connecting systems and the muscular systems of the ventricle and to a shortening of the *R–V* interval. Thus the conduction of the stimulation in the connecting systems and the ventricular muscle and the *R–V* interval at first, after a slower rhythm has set in, has improved, whereupon it slowed down again as a result of the progressing poisoning process, until by another halving this conduction of the stimulation improves again. The more rapid or slower conduction of the stimulation in the musculature of the ventricle, and the decrease and increase of the *R–V* interval, correspond with the increase and

decrease of the excitability of the ventricular muscle. This certainly shows the close relation existing between these two fundamental qualities of the heart muscle. For when the excitability of the ventricular muscle has decreased, the conduction of the stimulation cannot but grow slower: each successive level will be less sensitive to the stimulation as it comes on, viz. the latent stage will be lengthened for each level, or else the time which the stimulation requires to pass completely through the ventricular muscle will be longer.

With this conclusion the electrograms of the ventricle obtained directly after the halving of the rhythm apparently do not agree. The conduction of the stimulation immediately after the halving is rapid (the duration of the *R* is rather short), and one would expect the duration of the entire ventricular electrogram to decrease, but this is not the case; the duration of the complete ventricular electrogram has strongly increased. Here, therefore, another factor must be present causing the strong increase in the duration of the ventricular electrogram. We are facing the same question as in the post-compensatory systole. There also the conduction of the stimulus has improved and the duration of the ventricular electrogram has increased. Here also I found before the extrasystole the same antithesis between the rate of conduction and the duration of the electrogram. Whilst the rate of conduction had decreased, the duration of the electrograms of the extrasystoles had likewise decreased. Now this decrease in the duration of the electrograms before the extrasystoles may be attributed to a partly asystolic condition, and the antithesis thereby be solved if one desires to adhere to the principle that the electrograms as a whole are merely a product of the conduction of the stimulus. But if, for the antithesis in the rate of conduction of the stimulus and the duration of the electrogram immediately after the halving and in the post-compensatory systole, one tries to arrive at a solution in the same way, one meets with insuperable difficulties. We should have to assume that the normal systoles originate in contraction of part of the cardial musculature and that the true systoles of the whole ventricular muscle only manifest themselves in the slower rhythm. And this supposition seems to me to be quite incorrect. For how, then, is it to be explained that after an extra stimulation of the auricle the *R*-excursion for the normal, the extra and the post-compensatory systoles are perfectly of the same height, even in the monophasic leading off? If the normal and the extrasystoles were originated by a partly asystolic condition, and the post-compensatory systoles by contraction of the entire

musculature of the ventricle, the *R*-excursion of the latter ought to be larger than for the normal and extrasystoles. In my opinion these data would lead to attributing the *R*-excursion to a process different from the other part of the ventricular electrogram. If, searching in this direction, we wish to arrive at an explanation of the ventricular electrogram, we should attribute the rapid *R*-branch to a process, which can also come to full expression after shorter heart pauses, then the slow excursion, which succeeds it in duration and length, is dependent on the duration of the preceding pause. As a matter of fact the dualistic theory of the muscular contraction then forces itself upon us. In the same way as in the striated muscles a rapid, clonic, and a slow, tonic contraction may be distinguished, we should also premise these two ways of contraction for the heart muscle, and then we get a much clearer idea of the electrogram of the heart. The rapid *R*-branch would then be the electric expression of the rapid contraction of the heart muscle and the further part of the electrogram would have to be attributed to the slower tonic contraction. The rapid contraction would take place by way of initial shortening of the ventricular musculature and thereby regulate the pressure on the contents, whilst the tonic shortening would do the actual work by driving out the contents. The much longer duration of the latter process would necessitate a longer pause for this tonic shortening to arrive at its full development. Thus each systole is composed of a variable and a usually invariable part. The variable portion is in duration and length dependent on the foregoing pause; the invariable, or at least usually invariable part, also recovers its former state after shorter pauses. For this it is necessary to consider the first rapid contraction as *usually* invariable, because even now I have examples in which the first rapid shortening can also decrease. These instances relate to partly asystolic conditions, which I intend discussing separately.

The next series of records is still more adapted to give direct information with regard to the way in which the heart muscle contracts. In these experiments also I found after the poisoning an increase of the *P–R* interval and the *R–V* interval, as well as of the duration of the *R*. Again these values all decreased when (10 minutes after the injection of eight drops of a 1 % veratrin solution) the ventricular rhythm had been halved, increasing again as the poisoning progressed. The *R*-excursion increases in width, but does not split until 75 minutes after the injection. The duration of the *R*-excursion is then $1\frac{1}{4}$ time unit of $\frac{1}{5}$ second.

In the following 45 minutes three records were made and in them were consecutively R-excursions of $1\frac{3}{4}$, 2 and almost 3 time units. In the first of these records a splitting of the R-excursion is plainly to be seen, which comes more fully to expression in the two following records. The last of these records is represented in Fig. 6. We see

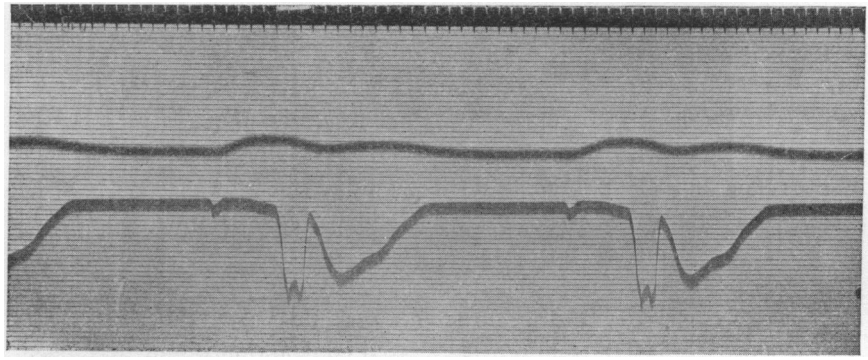

Fig. 6.

here a strongly pronounced splitting of the top, which I always saw after veratrin poisoning, when the broadening of the R had increased to a certain value. So long as the rapidity of the conduction is rather great the meanwhile increasing negativity of the apex of the heart is the cause that the R-excursion returns to the 0-line with one single

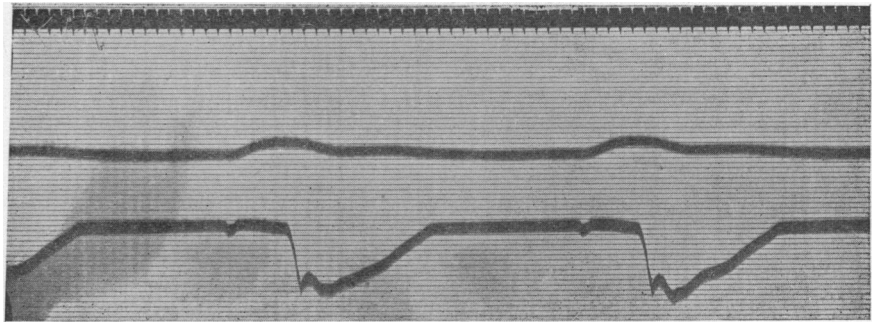

Fig. 7.

sharp top. Thus it seems quite clear that in reality the negativity of the base begins with a sharp point, and increases again subsequently, whilst then, the conduction being slow, this second increase is interrupted by the negativity of the apex, which has suddenly set in (see Fig. 6).

This conception is also confirmed by Fig. 7. I made this record 10 minutes later, after having previously thoroughly cauterised the apex by means of a red-hot needle. Thus, here we have an image of the negativity of the base of the heart. Here also we see a rapidly increasing excursion, followed by the entire slow excursion.

I am then of opinion, like Samojloff (6), Mines (7) and Borutteau (8), that the biphasic electrogram of the ventricle should be considered as the interference product of the negativities expressing themselves at the electrodes of the base and the apex. These two components, however, are in their turn each composed of a rapid initial excursion and a subsequent slow negativity. The rapid initial excursion we can compare with the action current of a striated muscle, the slow negativity being the electric expression of the tonic shortening. This latter way of shortening would accomplish the actual work required for the expul-

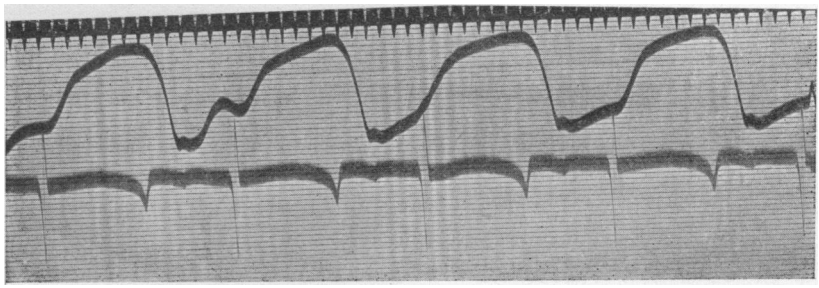

Fig. 8.

sion of the contents; by the former shortening the ventricular cavity is rapidly reduced and thus the pressure on the contents regulated.

On the view that the two polar components of the ventricular electrogram are each composed of a rapid initial excursion and a subsequent slow excursion, electrograms of the ventricle, commencing with a purely diphasic rapid excursion, are more easily explained. In Fig. 8 I represent such an electrogram. They are frequently seen in frogs' hearts, and it seems to me that they can only be explained if each of the polar components is composed of one rapid and one slow excursion. This form, I think, represents the pure diphasic ventricular electrogram. According to this conception the *S*-excursion would be caused by the electrogram growing more diphasic in form. Of the frog's heart of Fig. 8 record Fig. 9 was made 20 minutes after injection of five drops of a 1 % solution of veratrin. We see that the *P–R* interval and the

R–V interval have strongly increased as well as the duration of the *R*-excursion. The electrogram, which before the poisoning ended in the beginning of the diastole, now ends in the end of the diastole. The duration of the electric phenomena thus corresponds with the duration of the refractory period. Half an hour later the record of

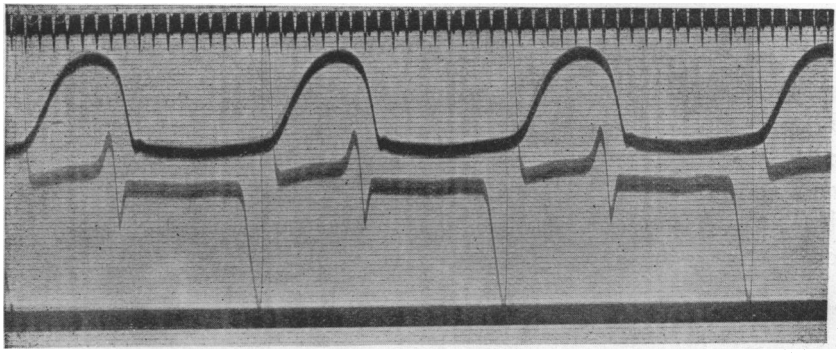

Fig. 9.

Fig. 10 is made. Here we see that the second auricular and ventricular systoles have disappeared. After the resulting longer pause the *R*-excursion of the following electrogram is of shorter duration; the *R* of the next electrogram after a shorter pause is again much broader. The same relation we find in these two ventricular electrograms for the

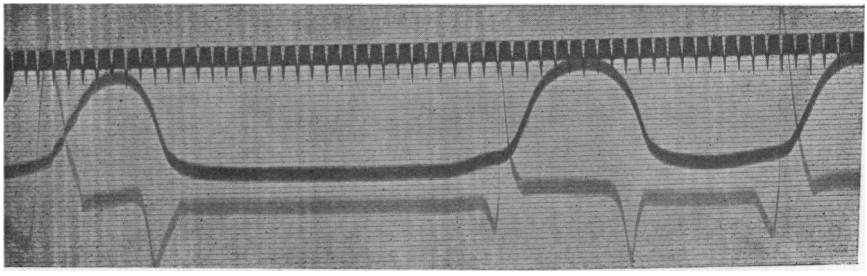

Fig. 10.

R–V interval. After the long pause this *R–V* interval is much shorter than after the short pause.

The direction of the *R*-excursions shows that the systoles are chiefly of the apex type. From this we see that in hearts *in situ* a negativity can be caused in the ventricle by the stimulation led from the auricle

along the normal conducts, which is preponderant in the apical part of the ventricle. In the record, taken an hour after the preceding one, we see a fine instance of systoles of the basic and the apical types side by side (Fig. 11). Between the second auricular systole and the succeeding ventricular systole there is a very long *P–R* period. The mechanic curve of the ventricle rises gradually, whilst the string shows a wavy line as a result of an alternating increase of negativity of the apex and the base, until finally an abrupt negative *R*-excursion sets in. The impression is made, as if at last the stimulation has found its way into the apical part. The descending line of this negative *R*-excursion extends some distance under the state of rest, whereupon there is an increased *T*-excursion; thus the connecting line between the *R* and the *T* had descended far under the 0-line. This curve in no single

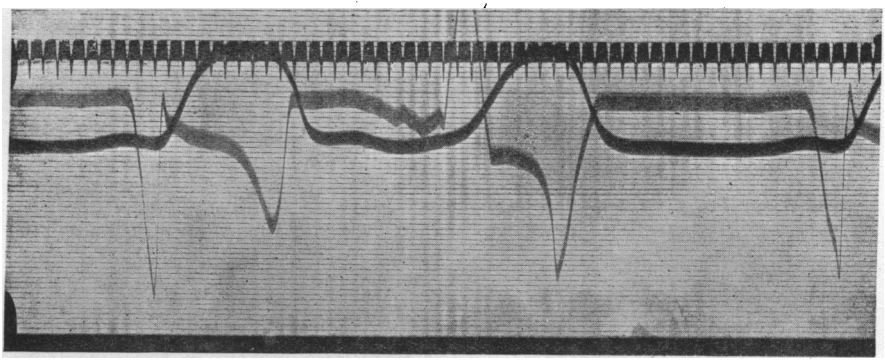

Fig. 11.

respect shows the difference from the extrasystoles of the mammals of the left-sided type. I also obtained such curves in frogs' hearts by stimulation of the heart point. Thus I am of opinion that this curve procures greater certainty than that of Fig. 10 in regard to the direction of the conduction of the stimulation in the ventricular muscle. From the curve of Fig. 10 we could only conclude that the negativity was stronger at the apex than at the base; for the second systole of Fig. 11 the negativity begins at the apex and proceeds in the direction of the base. We must therefore take for granted—which Seemann also already pointed out—that there is a direct connection between the auricle and the ventricular apex. The third systole has again been eliminated and still the resulting pause shows only a slight increase. For the beginning of the second *R* follows $\frac{23}{6}$ sec. after that of the

first, whilst the third R follows $\frac{26}{5}$ sec. after the second. This is caused by the long a–v (P–R) interval of the second systole. The first two systoles of Fig. 11 thus form a bigeminous group, composed of one systole of the base type and one of the apex type.

Theoretical Conclusions.

As early as 1892 Bayliss and Starling(9) considered the ventricular electrogram, which is mostly composed of two similarly directed excursions, as the resultant of the negativities effected at the base and the apex of the heart. The negativity first begins at the base and there also is continued the longest, so that two similarly directed excursions are originated. After warming the base of the hearts of frogs and dogs they obtained two excursions in opposite directions and after warming the apex two excursions in the same direction. This would be the result of the fact that in the former experiment the duration of the base component was shortened by the more rapid conduction and in the latter experiment the apex component.

After the discovery of the bundle of Gaskell, Kent, His and on the ground of ontogenetic considerations Gotch(10) put forward a theory on the origin of the ventricular electrogram. He premises that in the ventricular musculature the stimulation proceeds from the bundle of His, through the papillary system to the apex and thence back again along the outer longitudinal layer to the base in the region of the aorta. The first excursions (G, R, S) would be caused by the negativity, which proceeds along the papillary system in the direction of the apex, whilst the T-excursion would be caused by the base in the region of the aorta becoming again negative. Between the two excursions the two leading-off poles would be iso-electric during the contraction of the actuating apparatus (Treibwerk). This theory, which was also adopted by Kraus and Nicolai, is thus completely based on the manner of transmission of the conduction wave, whilst it attributes the two ventricular excursions to the negativity of various muscle complexes. It neglects, however, the fact that the T does not always follow the same direction as the R, but may just as well follow an opposite direction. Moreover, if it is premised, that the base in the region of the aorta becomes negative during the T-excursion as a result of the stimulation returning from the apex, the stimulation transmitted in the direction of the arterial system must in a frog render the bulbous aortae negative after the T. According to this conception the bulbous-excursion would always have to appear after the T-excursion. Now

I have observed very often the bulbous-branch in my electrograms of the frog's heart, but always between the *R* and the *T*-excursion and then mostly nearest the *R*.

Einthoven(11) explains the *T*-excursion by the base remaining negative the longest; this he also points out emphatically in his latest communication.

A. Hoffmann(12) and Seemann(1) took the *R*-excursion to be an expression of the conduction, the *T* an accompanying phenomenon of the contraction process.

Latterly the old conception of Bayliss and Starling has been re-established by Samojloff, Mines and Borutteau. Thus these experimenters consider the ventricular electrogram as an interferential (interference) product of the negativities occurring at the base and the apex.

Samojloff arrived at this conception by his well-known researches, in which he locally slowed down the conduction of a frog's heart by making a cross section in the ventricle; the two negativities of the base and the apex then set in separately and one after the other. Some time afterwards this conduction recovered its former state, so that the two separate components again covered each other and produced a biphasic ventricular electrogram.

By vagus stimulation and muscarin poisoning Samojloff saw the *T* change in a negative direction. Mines repeated the old experiments of Bayliss and Starling by warming the base or the apex of frogs' hearts. In the first case he saw the positive *T* become negative, whilst a negative *T* grew even more strongly negative; in the latter experiment, by warming the apex, he saw a negative *T* become positive and a positive *T* even more strongly positive. Likewise Mines studied the influence of different ions on the shape of the ventricular electrogram in experiments on frogs' hearts in a circulating fluid. Borutteau studied the duration of monophasic ventricular electrograms, in which he compared the duration of monophasic electrograms by placing one electrode on the unimpaired ventricular base and one on the wounded middle-part of the ventricle, with the duration of monophasic ventricular electrograms, in which one electrode was placed on the unimpaired apex and the other on the wounded middle-part of the ventricle. These two records he made with different hearts in immediate succession, making at the same time a biphasic record by applying the leading-off electrodes to the apex and the base respectively. In the case of a positive *T* for the biphasic ventricular electrogram he then always found

that the monophasic base electrogram lasted longer than the apex electrogram, and in the case of a negative *T* just the reverse. This result he also verified by records taken after muscarin poisoning and vagus stimulation.

Thus these three investigators arrived at the same conclusion along different lines, in which, indeed, Einthoven also based his explanation of the *T*-excursion. And this conception seems to me quite correct. The diphasic ventricular electrogram gives the sum of the negativities ending in the base and the apex, just as in a skeleton muscle in diphasic leading off during a twitch the sum of the negativities on the two leading-off poles is obtained.

In a striated muscle, however, these negativities during a twitch are of very short duration, so that if the spot of stimulation is outside the leading-off electrodes first the one and then the other of the leading-off poles becomes negative. If on the contrary the spot of stimulation is between the leading-off poles, there also a summing up takes place of the negativities on the two leading-off poles. Thus Piper(14) found a fairly complicated curve, when with an indirect stimulation of the fore-arm flexors he placed one of the leading-off electrodes under the nervous equator and the other above it. He then found that the negativity came first to expression on that one of the leading-off electrodes which was placed nearest the nervous equator. Now in the heart we obtain in the beginning of the ventricular electrogram a rapid excursion as an expression of the basic negativity, whilst at the end of the ventricular electrogram usually another excursion is caused in the same direction. Between the two excursions the string as a rule is in the 0-line, which means an equipotentiality of the two leading-off poles. Monophasic leadings off for the base and the apex show us that there the negativities are about of as long duration as the entire biphasic ventricular electrogram (from more exact records by Borutteau it appears that the negativity at the apex is of somewhat shorter duration than at the base). The monophasic excursion of the apex has an opposite direction from that of the base. The two similarly directed excursions of the diphasic ventricular electrogram thus mean that the negativity first starts at the base and is there of longer duration than at the apex. The negativity at the apex thus begins at the top of the *R*-excursion. In those cases, in which the *T* is negative, the negativity at the apex will consequently have been of longer duration than that at the base. The explanation of Gotch does not provide for this possibility. That, moreover, the course followed by the stimulation

through the heart is not of such preponderant significance as Gotch, Kraus and Nicolai attribute to it, is proved by the fact that extrasystoles, resulting from an extra stimulation of the ventricular base, produce ventricular electrograms with a rapid initial excursion (*R*) and a slower excursion (*T*) at the end. The changes in these electrograms are merely a result of the change in the place where the stimulation enters the ventricular musculature, so that the starting point of the ventricular negativity in respect to the leading-off poles has changed places; another cause of the changed electrogram of the ventricular systole is the fact that the beginning of the extrasystole falls earlier in the heart period. This latter cause alone is sufficient to change the electrogram of the ventricular extrasystole, if we effect the extrasystole by an extra stimulation from the auricle, so that then the place of entrance of the stimulation is the same as for the normal systoles. As in both cases the negativity begins at the base, the difference between ventricular extrasystoles excited from the auricle and those excited from the ventricular base is unimportant. This difference exists only in the changed height of the *R*-top after stimulation of the ventricular base.

That the complicated muscular structure of the ventricle is not responsible for the form of the ventricular electrogram, is already proved by the fact that other partitions of the heart of less complicated construction, show the same rapid initial excursion and slow final excursion.

But if now we consider the diphasic ventricular electrogram as an interference product of the negativities at the base and the apex, the question arises, whether we should consider each of these pole negativities as a mere expression of the conduction of the stimulation. Between the beginning and the end of the basic negativity there is a space of about $1\frac{1}{2}$ sec. Thus $1\frac{1}{2}$ sec. would have to elapse before all the basic muscle-cells had been reached. If then we consider the basic component (and also the apical component) as a mere expression of the conduction of the stimulation, the rapidity of the transmission for the small frog's heart would have to be very slight indeed. In order to realise how $1\frac{1}{2}$ sec. can be required for the stimulation to travel this short distance we should have to premise for the heart conditions entirely different from those existing in the striated muscles. Moreover, this representation to begin with does not seem correct to me, because then the various muscle fibres of the heart would contract one after the other and would in that case co-operate very imperfectly indeed towards the great duty to be fulfilled by the heart.

If we wish to adhere to the conception that the electro-cardiogram as a whole is an expression of the conduction of the stimulation, the stimulation, coming from the sinus venosus, would already have reached the ventricle, before it had been conducted through the entire auricle, for the rapid *R*-branch coincides with the slow excursion of the auricle, and likewise the bulbous would have been reached some time, whilst the stimulation was still being conducted through the chamber.

Another conception seems to correspond better with these facts. If we premise that the base and apex components are each composed of a rapid initial excursion and a subsequent slow negativity, we can consider the rapid initial excursion as the expression of the conduction of the stimulation, like the action current of the striated muscles. The slow negativity which follows would then be the electric equivalent of the slow tonic contraction, by which the actual work of the ventricle is done. According to this conception alone the ventricular electrograms also, as represented in Figs. 8 and 9, beginning with a rapid diphasic *R*-excursion, can be construed. Interference of two slowly proceeding basic and apical negativities does not explain such ventricular electrograms. That each of the components is composed of a rapid initial excursion and a subsequent slow excursion, is also shown by Figs. 6 and 7. In Fig. 6 the conduction of the stimulation has grown so much slower by veratrin poisoning that the initial top is fully seen and the slow basic component begins already before the negativity at the apex sets in. The monophasic electrogram of Fig. 7 shows this same rapid initial top with the entire slow basic negativity. The fact that this slow basic component in other cases also where the conduction of the stimulation has grown slower, shows itself as a doubling of the top, is of great importance. Thus we repeatedly meet with this doubling of the top in extrasystoles of mammal hearts. Here also there is a slowing down of the conduction of the stimulation (broadening of the *R*-excursion). If this conception is correct the ventricular electrogram is composed of a rapid *R*-excursion as the expression of the conduction of the stimulation throughout the ventricular muscle, which causes all the fibres of the ventricular muscle to shorten rapidly, which shortening is followed by a slow negativity as the expression of the tonic work of expulsion of the ventricular musculature. The rapid contraction would regulate the pressure on the contents of the ventricle within a short time. The *S*-top would then be a result of the fact that the rapid initial excursion rather comes to expression as a biphasic excursion.

By the longer duration of the slow tonic excursion the latter is more prominent after a longer pause, whilst after a shorter pause the tonic excursion is strongly reduced. These relations we find for the post-compensatory systole, in which the tonic excursion has been strengthened, and in the extrasystole, in which it has been shortened and reduced. The *R*-excursion of shorter duration is as high for the extra and post-compensatory systoles as for the systoles of the normal rhythm. Vagus stimulation and muscarin poisoning check the tonic shortening, and thus we see as a result not the *R*-excursion but the *T*-excursion reduced. By warming at one of the leading-off poles the tonic contraction is here reduced, so that at the pole which is not warmed the *T*-excursion gradually predominates.

All these well-known facts seem to me to point out that the *R*-excursion and the *T*-excursion originate in different processes.

Summary.

After poisoning the frog's heart with veratrin, the rhythm is slowed, the duration of the *R*, of the *P–R* interval and the *R–V* interval are increased. The pauses between the mechanograms increase, those between the electrograms of the heart decrease. (The *T* ends later in the diastole, the *R* begins sooner before the systole.)

After halving the rhythm, the duration of the *P–R* interval, the *R–V* interval and of the *R* decreases again. The duration of the *R* gives a measure of the velocity of conduction in the ventricle, the *P–R* interval of the velocity of conduction through the auricle and conjunction systems between auricle and ventricle, the *R–V* interval gives a measure of the latent stage of the contraction of the ventricle. In this way these three values increase after poisoning with veratrin and decrease again after the halving of the rhythm; in a later stage after halving the rhythm, when the poisoning proceeds, these values increase again. As intermediate stage between the normal and the halved rhythm heart-bigeminus exists; then every third pulsation falls out.

The *P–R* interval after the long pause is short, after the short pause, long. (Elsewhere I have shown that the duration of the *R* also follows this rule.) After poisoning with veratrin, the excitation in the ventricle may start from the apex of the heart and thus there may be alternate systoles beginning from the apex and from the base of the ventricle. After considerable slowing down of the conduction in the ventricle, the broad *R*-top may split in two. Monophasical registration gives a quick beginning top after which a slower one follows.

This supports the view that the electrogram of the ventricle is the result of two negativities with opposite signs, which appear at the base and the apex. (Mines, Samojloff, Borutteau.) But each of these negativities would consist of a quick beginning and of a slower following negativity. In this way the electrograms of the ventricle with purely diphasical *R* would be more comprehensible. The acceleration of conduction after the halving of the rhythm and the great increase of duration of the electrogram of the ventricle cannot be satisfactorily explained on the view that the electrogram is only a result of the propagation of the excitation. This is also true of the electrograms of the post-compensatory systoles after extrasystoles (the duration of the electrogram is increased, the velocity of the conduction also). Elsewhere I have shown that extrasystoles are only systoles which begin earlier in the heart period and have no particularities; only the velocity of conduction through ventricle has slowed down and a fixed variability of the slow *T*-top takes place. We find this slowing down of the conduction and these same variations of the *T*-top for all systoles which begin at an earlier moment after a former systole. So the second systole of heart-bigeminus begins at an earlier moment after the former systole, compared to the first systole. We can say, that the halved rhythm is there, but every systole is followed by a premature systole. And this premature systole has the same peculiarity as an extrasystole.

If this second systole begins at the apex, the *R* is inverted and the *T* grows in positive direction; if it begins at the base, only the *T* grows in negative direction (a positive *T* decreases and a negative one increases). In both cases the duration of the *R* increases. The extrasystoles show these same variations.

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