Physiology. — "*A study of the heartmuscle according to the pharmaco-physiological method.*" By Dr. S. DE BOER. (Communicated by Prof. G. VAN RIJNBERK).

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

Introduction. When studying the function of the heart we can do so in the first place according to the usual physiological methods. In the second place we can examine the heart according to the pharmacological method by making poisons exert influence upon it. We derive the knowledge of the disturbances of the heart-rhythm especially from the use of such poisons as incite the heart-muscle to greater activity, consequently the poisons of the groups digitalis, antiarine and veratrine. All these poisons, if not applied in too great a dose, cause an increase of the dimension of the systoles, after which suddenly halving of rhythm can occur. This was shown by BOEHM (1) for digitalis, by v. BEZOLD and HIRT (2) and also by BOEHM for veratrine, by HEDBOM (4) and STRAUB (5) for antiarine. This halving of the rhythm was caused by an increase of the duration of the refractory period and at the same time of the *a-v*-interval. It took first place at the ventricle and afterwards at the auricle. At last the heart stood still in maximal systole. I refer for my own investigations into the modifications of the heart-rhythm to the list of literature at the conclusion of this communication (6, 7, and 8).

Besides these physiological and pharmacological methods the combined pharmaco-physiological method can, in my opinion, be of great use for the study of the general physiology of the heart. I understand by this the application of the usual physiological methods to the *poisoned* heart, in consequence of which the irritability, conductivity and contractility have changed. I applied this method already previously, when by refrigeration of the sinus venosis I reduced the ventricle of a frog's heart, pulsating, after being poisoned with veratrine, in the halved ventricle-rhythm, to the normal rhythm. At the same time I made some investigations into frog's hearts poisoned with veratrine by means of extra-stimulation. In this way I could reduce a ventricle, pulsating in the halved rhythm, to the normal twice as rapid rhythm, by an extra-stimulation at the end of the diastole. I have now systematically applied this method, i.e. the application of extra-stimulations during the different time-moments of the heart-period of hearts poisoned with veratrine, and obtained in this way a rich material of curves. I arranged my experiments,

as I described already previously, and irritated by means of opening-induction strokes (movement of the signal upward) whilst the closing strokes were blended.

Every frog's heart was examined before the injection of veratrine by extra-stimulation, whilst after the poisoning this method was continued for a few hours. The number of experiments made in this way amounts to more than 200.

1. *Extra-stimulation of the heartpoint.*

I succeeded in bringing about artificially by extra-stimulations the modifications of rhythm, occurring spontaneously, previously described by me. As in these transitions the duration of the refractory-period plays an important part, it is of importance to know how it behaves after the poisoning. A great number of experiments made in this respect have taught, that its duration increases after poisoning with veratrine. I found even, at a certain stage of the poisoning before the halving of the ventricle-rhythm began, this ventricle refractory till far in the pause. After the halving the ventricle-muscle was then irritable again already during the diastole. This fact can only be explained, if we admit 2 components of the refractory stage after the poisoning.

1. *The periodical refractory-stage* i.e. that part that is contributed during a special heart-period by the contraction of the ventricle-muscle during this heart-period.

2. *The residue refractory-stage*; this second component is caused by the fact that, at the beginning of each systole, the heart-muscle is not entirely restored.

The farther the poisoning advances, the more this 2nd component increases, till the halving of the ventricle-rhythm is completed. The latter occurs as soon as:

$$\frac{\text{the duration of the refractory-stage}}{\text{the duration of a sinus-period}} \text{ surpasses } 1.$$

I called this *the relative duration of the refractory-stage.*

As soon as the relative duration of the refractory stage is about 1, I can discretionally modify the rhythm of the ventricle by an extra-stimulation. Every modification of rhythm that can occur spontaneously, can also be obtained by means of an extra-stimulation.

As an example of my material of curves the following experiment may serve.

On the 30th of Aug. 1915 (curvesheet 60) I suspended a frog's apex ventriculi in the way I described already. First I noted down about 100 systoles of the unpoisoned heart. By extra-stimulation of the

apex it was found to be perfectly irritable during the entire diastole. Afterwards I injected 5 drops of a solution of veratrine 1% under the skin of the thigh.

During the diastole the irritability gradually decreases, so that in the end, with an equal strength of the stimulation as before the injection, I can only during the pause obtain extra-systoles which are much smaller than the systoles of the normal rhythm. The frequency of the systoles diminishes somewhat. About half an hour after the injection halving of the ventricle-rhythm begins. After the heart has executed a few systoles in this halved rhythm, I apply an induction stroke at the end of the diastole. By this stroke the normal, twice as rapid rhythm is restored (vide fig. 1)[1]). This can be explained as follows.

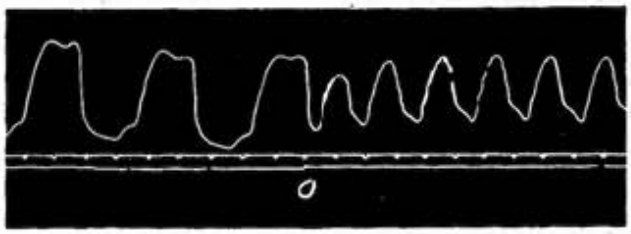

Fig. 1.

Whilst the ventricle is pulsating in the halved rhythm, the pauses between the ventricle-systoles have become much longer. This causes the residue refractory-stage to decrease, because the ventricle-muscle can better restore itself during the lengthened pauses. Yet the normal rhythm does not return, because the periodical refractory-stage has increased in duration. The lengthening of the periodical refractory-stage is a direct consequence of the enlargement of the systoles. The result is then, that the total refractory-stage has not yet diminished in duration, as long as the halving of the ventricle-rhythm lasts. I expressed this in a previous communication by observing, that the increase of size and duration of the systoles in the halved rhythm captivates the ventricle in its own rhythm. If now, at the end of the diastole, I apply an extra-stimulation (at *O*) an extra-systole is caused, which is much smaller, because the pause that immediately

[1]) All figures have been reduced. The figures 1 to 6 included, belonging to the same heart, have not been reduced in the same measure. The distance between the stimulation-signal and the time-signal, which is equal in the original rows of curves is unequal in these figures. This allows us to judge of the different degrees of reduction.

precedes, is considerably reduced. Consequently the periodical refractory-stage of this extra-systole is much smaller than with the systoles of the halved rhythm. For that reason the total refractory-stage during this extra-period has become much shorter than during the periods of the halved rhythm.

After this one preceding, shorter pause the residue refractory-stage has of course not yet strongly developed itself. It increases only by accumulation, when the ventricle has executed a few systoles in the normal rhythm. Consequently it is clear that the total refractory-stage during the extra-systole is shorter than during the systoles of the preceding halved rhythm. And therefore the next following normal "Erregung", coming from the auricle, causes a systole in the ventricle. But this systole is also again smaller under the influence of the preceding short pause, so that also after this systole the next following impulse coming from the auricle causes a systole of the ventricle. Thus the normal, twice as rapid rhythm continues, till, by increase of duration of the residue-refractory-stage, the total refractory-stage has been lengthened so much, that this rhythm can no longer be maintained. In our present case the normal rhythm continued during 16 systoles, and then changed into bigeminus-groups alternating with trigeminus ones. This bigeminy passes into the halved rhythm. By an induction-stroke at the end of the diastole I convert this halved rhythm into bigeminy. When this bigeminy has lasted for about two minutes, I apply an extra-stimulation to the apex ventriculi just before the end of the diastole of the first large curve of a bigeminus-group (fig. 2) [1]).

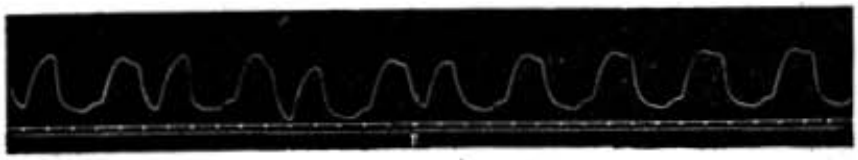

Fig. 2.

The extra-systole that is occasioned then, is a little smaller than a 2nd systole of the bigeminus-groups, and the pause after it is a little longer than the pauses between the bigeminus-groups. The next following systole is thereby somewhat enlarged, so that now the halved rhythm ensues. Now the total refractory period of each systole is of too long a duration for another systole to follow after it with the interval of the normal rhythm, as is the case with the

[1]) In the figures 2, 4, 7 and 8 the signal-oscillation, indicating the stimulation is a little too small. By adding an arrow (↑) I have indicated more exactly the moment, when the stimulation was applied.

bigeminus-groups. During this halved rhythm the total refractory period is thus of a longer duration than during each first systole of the bigeminus-groups. At the end of the diastole of the 4th curve in this halved rhythm I effect an extra-systole by an extra-stimulation (vide fig. 3 at *O*). This extra-systole is followed by a normal

Fig. 3.

systole, but the then following impulse of the auricle, when reaching the ventricle, is not answered by the latter.

The then following impulse occasions, it is true, again a ventricle-systole, but this systole is a little smaller and of shorter duration than the preceding systoles of the halved rhythm. The following auricle-curve descends a little deeper down from the top of the first systoles of the bigeminus-groups that are now following, than with the systoles of the halved rhythm. Consequently we have shortened the total refractory period of this ventricle-systole, compared with the duration of the refractory-periods of the halved rhythm. The consequence of this is that still another systole can follow, after which one ventricle-systole falls out, so that bigeminus-groups appear, among which occurs accidentally a trigeminus-group. If I had applied the extra-stimulation earlier in the diastole, the normal rhythm would have appeared. The extra-systole would then, proportionally to the greater diminution of the preceding interval, have been smaller, so that just as in fig. 1 the normal rhythm would have followed. This appears distinctly, if during the 6th group after the last of fig. 3 (vide fig. 4) I apply an extra-stimulation at an earlier

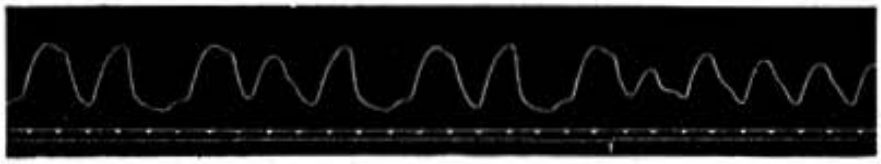

Fig. 4.

period of the diastole of the first curves of the bigeminus-group (at ↑). The extra-systole is then small, and the normal rhythm is restored, continues during 15 systoles, and changes then into some bigeminus-groups and afterwards into the halved rhythm.

Two groups previously I had applied an extra-stimulation a little later; the extra-systole is now larger, but the next systole is still larger, apparently, because the preceding *a-v*-interval has been lengthened, and consequently the systole occurs later (vide fig. 4). A more accurate mensuration shows us that in reality this systole begins at a later moment. This fact especially also counteracts the occurrence of the normal rhythm.

When now the restored normal rhythm of fig. 4 has passed again into the halved rhythm, I execute here after the 6th systole of the halved rhythm a second method of converting from the halved rhythm into the normal one (vide fig. 5).

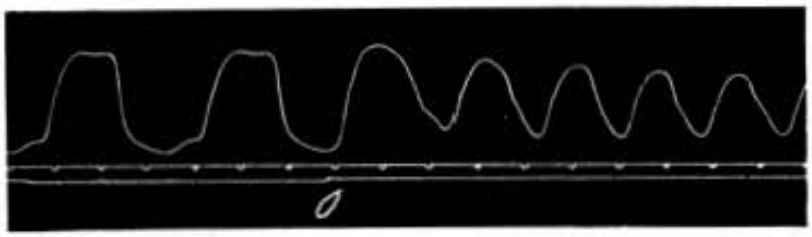

Fig. 5.

I described already previously, how the halved rhythm can be converted into the normal one by an extra-stimulation at the end of the diastole. I had then to apply the extra-stimulation at a special moment of the diastole to make the conversion succeed. So I applied, also with this heart, in Fig. 1 (at *O*) the extra-stimulation towards the end of the diastole. If I had applied the extra-stimulation at an earlier moment of the diastole, it would either have had no effect, and consequently have permitted the halved rhythm to continue undisturbed, or it would have produced a still smaller extra-systole. The next impulse however would then, after this smaller extra-systole, have produced later a systole which would for this reason have become too large to let the normal rhythm continue. If I had on the contrary applied the extra-stimulation later, the extra-systole itself would have proved to be larger, and would have become too large for the restoration of the normal rhythm. The halved rhythm would have continued (Vide fig. 8) or heart-bigeminy might have occurred as in Fig. 3.

It is therefore obvious, why I had to irritate the ventricle exactly at a special moment in order to obtain restoration of the normal rhythm.

TIGERSTEDT, STRÖMBERG and ENGELMANN could also bring about a twice as strong frequency of the pulsations by an extra-stimulation during the diastole in their experiments on the sinus venosus and

heart-veins. These investigators have not been able to explain this phenomenon. It is certainly peculiar that I myself, in the beginning, found this conversion of rhythm only by extra-stimulations applied at a special moment of the diastole. The cause of this conformity —for in the beginning I made these experiments without being acquainted with the investigations of the above-mentioned authors— we must evidently find in the fact, that we are always accustomed to apply the stimulations during the diastole or shortly afterwards, but with few exceptions only in the end of the pause and certainly not of the long pauses that occur with the halved rhythm. And after-all there is a 2nd moment of the heart-period in which I can apply an extra-stimulation with as much success in order to restore the normal rhythm. *If I apply namely in the latter part of the pause, or in the beginning of the auricle-systole after the pause, an extra-stimulation either to the apex ventriculi or to the base, the normal rhythm restores itself also from the halved one* (vide Fig. 5 at 0). The extra-stimulation now causes an extra-systole, which happens to be rather large. Its great height may be explained by the fact that we register now at the same time a shortening of the ventricle- and the auricle-musculature. The fact that the ventricle is less full may perhaps likewise exercise some influence. This extra-systole occurs now at an earlier moment than the normal ventricle-systole of the halved rhythm would have appeared. With the systoles of the halved rhythm the second auricle-systole falls at the end of the systolic plane. With this extra-systole the next auricle-systole occurs at the end of the diastole, and can for this reason be succeeded by a ventricle-systole, which is small on account of the short preceding interval, and introduces for this reason the normal rhythm as in Fig. 1.

Here in Fig. 5 the normal rhythm is introduced by the normal physiological "Erregung" at the end of the diastole of a large extra-systole. The two experiments can be executed equally easily. It is consequently evident, that in two indicated places we can, during the period of the halved rhythm, by extra-stimulation of the ventricle-muscle convert this halved rhythm into the normal one. This restored normal rhythm passed after twelve systoles into bigeminy, which I converted again into the normal rhythm during the third group by an extra-stimulation, which was applied a little earlier in the diastole. After twelve systoles this normal rhythm changed again spontaneously into bigeminus-groups (as in Fig. 4). After about 3 minutes I converted these bigeminus-groups into the normal rhythm by an extra-stimulation, which was applied towards the end

of the diastole of the first systole of a group (vide Fig. 6 at 0).

This restored normal rhythm continues now during 95 systoles, and passes then again into bigeminy. After about one minute I

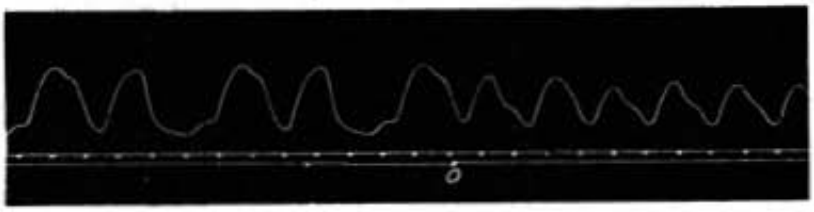

Fig. 6.

convert this bigeminy again into the normal rhythm, as I did in Fig. 4 and 6. This normal rhythm continues now for over half an hour, whilst the dimension of the systoles gradually decreases. Then the experiment is stopped.

Consequently with this frog's heart after the poisoning with veratrine we have converted:

1. The halved rhythm in two ways into the normal one by an induction-stroke (Fig. 1 and Fig. 5).
2. The halved rhythm into bigeminy (Fig. 3).
3. Bigeminy into the halved rhythm (Fig. 2).
4. Bigeminy into the normal rhythm (Fig. 4 and 6).

Consequently we can discretionally with a heart the ventricle of which pulsates in the halved rhythm, convert this rhythm either into the normal twice as rapid rhythm or into bigeminusgroups. Therefore we have to regulate the dimensions of the systoles by interfering at special moments of the heartperiod with the stimulant. These dimensions depend on the duration of the preceding pause.

Consequently if we obtain the normal rhythm, after having applied, at a special moment of the diastole, during the halved rhythm, an extra-stimulation, then we can obtain ventricle-bigeminy by applying the extra-stimulation a little later.

The experiments, in which I converted ventricle-bigeminy into the normal rhythm by an extra-stimulation in the diastole of the first curve of a group, which, consequently, produces an extra-systole, before the 2nd curve would have begun, are entirely in conformity with this view.

The difference in dimension between the ventricle-systoles of the halved rhythm and those of the normal one is very great. The dimension of the first systole of the bigeminus-groups is a medium between these. It is always smaller than the ventricle-systoles of the latest halved

rhythm. This appears distinctly from Fig. 2 and 3. This diminution is likewise apparent in Fig. 7.

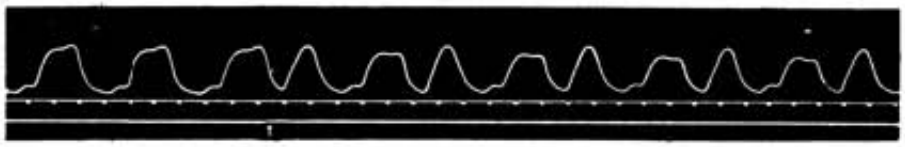

Fig. 7.

Here I applied to a frog's heart, pulsating after the poisoning in the halved rhythm, an extra-stimulation (at ↑) at the end of the diastole, the consequence of which was an extra-systole. The next following systole and further the first systoles of the bigeminus-groups are then visibly reduced. After two minutes this bigeminy spontaneously changes into the halved rhythm. If now a little earlier in the diastole, I cause an extra-systole, (vide Fig. 8 at ↑) the

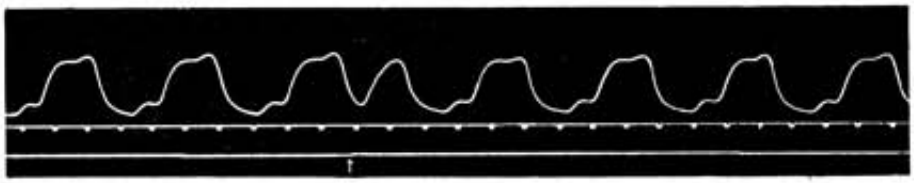

Fig. 8.

following systole is not sufficiently reduced to obtain bigeminus and the halved rhythm continues. But at the same time the extrasystole is not little enough to restore the normal rhythm.

2. *Extra-stimulation of the basis ventriculi.*

As in these series of experiments the stimulant was placed near the atrio-ventricular-limit, the results deviate somewhat from those that have been described above. I shall illustrate this by a few examples. In Fig. 9 I have caused at 1 an extra-pause without

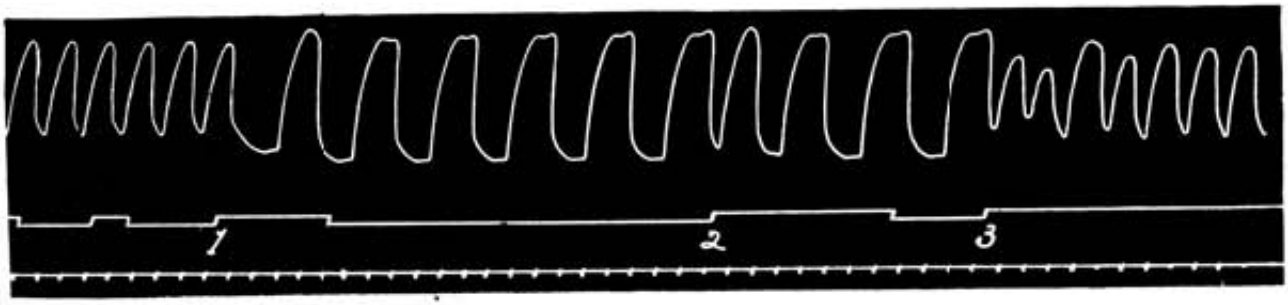

Fig. 9.

extra-systole of the ventricle by an extra-stimulation (the stimulation that I applied three systoles earlier, and that took place at an earlier moment of the heart-period, evidently reached the auricle during its refractory stage). The strongly increased postcompensatory systole fixes the rhythm of the ventricle in the halved one. At 2 I applied an extra-stimulation at the end of the diastole, which caused a rather large extra-systole without compensatory pause. If on the contrary I apply the extra-stimulation at 3 earlier, a smaller extra-systole follows, so that the normal rhythm is restored. During the 26th systole of this restored normal rhythm I convert this in the usual way again into the halved one. The 4th systole of this rhythm yet partially is to be seen at Fig. 10. At 1 the normal rhythm is not restored, at 2 it is indeed. After what has been said before this is obvious. At 3 I cause an extra-pause without ventricle extra-systole, but I prevent the return of the halved rhythm (as at 1 of Fig. 9) by stimulating again in this extra-pause at 4; by doing so I make a new extra-systole occur, which is smaller than the post-compensatory one would have become. For this reason and likewise because it comes earlier the normal rhythm is retained. The next-following impulse, coming from the auricle, consequently reaches the ventricle later after this extra-systole, than it would have arrived after the post-compensatory systole, if I had omitted the stimulation.

A place may still be given in this series to Fig. 11. In this heart (curvesheet 104) ventricle-bigeminy occurred half an hour after the poisoning. After a few minutes I convert at 1 of Fig. 11 this bigeminy into the normal rhythm by an induction-stroke at the end of the pause between 2 groups. The proportions under which this conversion is brought about, are not so simple here.

The extra systole comes here in the place of the first systole of a bigeminusgroup. But now the systole, following after the extra-systole, is wider than the second systole of a group, and has consequently a greater periodical refractory-stage. Consequently we should not expect after it another systole with a short interval. Yet this happens, the normal rhythm is even promptly restored. We find the cause of this phenomenon in modifications of the *a—v* interval. A little measurement teaches us namely, that the *a—v*-interval of the systole, succeeding the extra-systole is considerably abbreviated namely about $^1/_2$ second. The slight lengthening of the duration of the ventricle-systole by no means counter-balances this abbreviation of the *a—v*-interval, so that the auricle-systole, succeeding this ventricle-systole, can easily be followed by a new ventricle-systole.

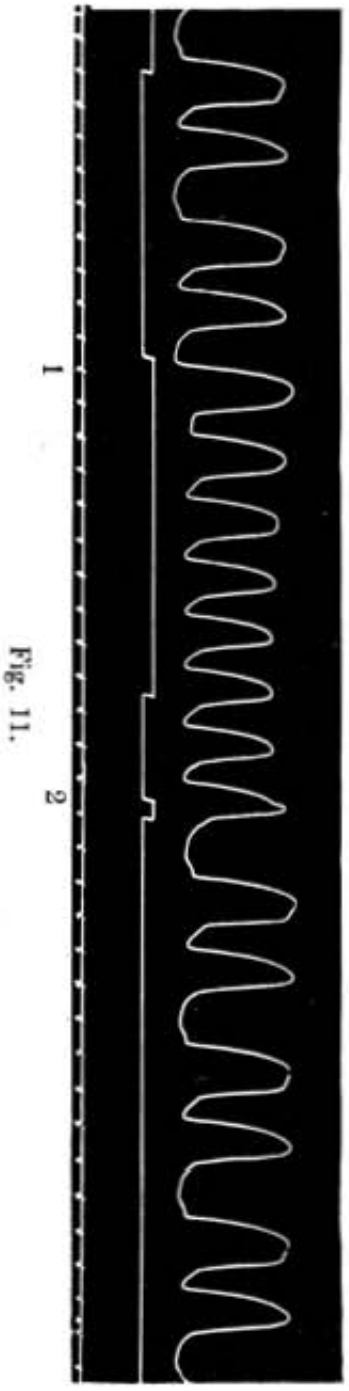

Fig. 11.

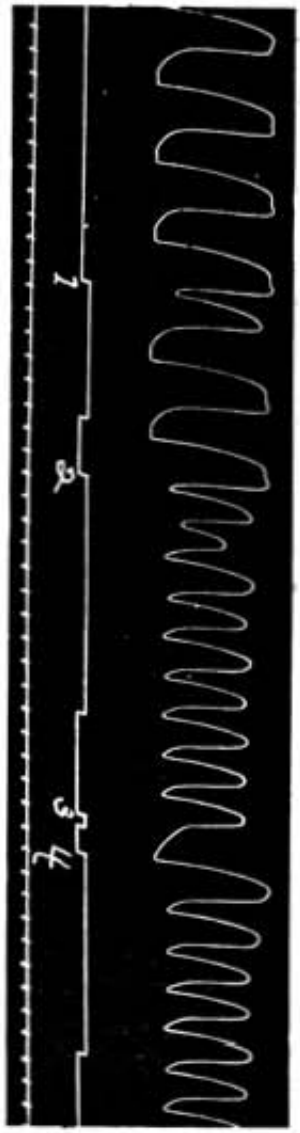

Fig. 10.

At 2 of Fig. 11 after the induction-stroke there occurs an extrapause without extrasystole of the ventricle, after which the ventricle-bigeminy appears again.

3. *Extra-stimulation of the auricle.* (Fig. 12).

Of this row follows here a figure in which I reduced a frog's heart (curvesheet 99) pulsating in the halved rhythm to the normal

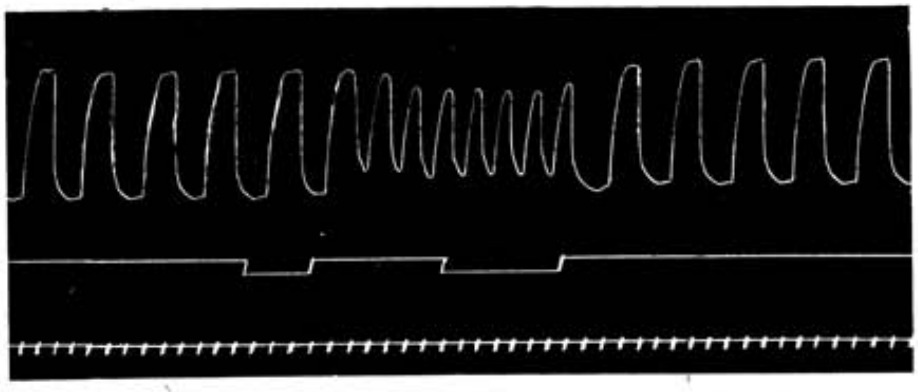

Fig. 12.

twice as rapid one, and the latter again to the halved rhythm. After the preceding remarks the explanation of this fact is obvious.

A short remark about the *a—v*-interval may still follow here. In my third communication about the heart-rhythm I have already shown experimentally, that the *a—v*-interval consists of 2 parts viz.:

1. Time of conduction along the systems of connection,
2. period of latent stimulation of the ventricle.

The experiments described before give again an entire affirmation of this fact. If namely I can convert the halved ventricle-rhythm into the normal one, by an induction stroke, it is certain that during the halved rhythm after every auricle-systole the "Erregung" reached the ventricle, but every 2nd systole recoiled, because the ventricle was then refractory. We find now during the halved rhythm the *a-v*-interval shorter than during the normal one. The cause of this cannot be found in a difference in the times of conduction along the systems of connection. For in both rhythms the stimulation after every auricle-systole is conducted along these systems. The shorter *a-v*-interval consequently originates in the fact, that in this rhythm the duration of the latent stimulation is shorter than during the normal twice as rapid rhythm. After the longer pauses of the halved rhythm the duration of the latent stimulation is consequently abbreviated.

The bigeminusgroups also distinctly explain this question. With these every normal physiological "Erregung" is conducted to the ventricle, for I can convert these groups into the normal ventricle-rhythm. The *a-v*-interval before the 2nd systole however is considerably longer than that before the first systole. Here this difference is likewise caused by the difference of duration of the stage of the latent stimulation.

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Astronomy. — *"Short account of some works by* BENSAUDE *upon the knowledge of astronomy and navigation in Portugal at the time of the great discoveries in the* 15^{th} *and* 16^{th} *centuries, presented to the Academy by the author."* By Prof. H. G. VAN DE SANDE BAKHUYZEN.

(Communicated at the meeting of March 25, 1916).

During the 14^{th} and 15^{th} centuries, the Portuguese, as is well known, made a number of important voyages along the west coast of Africa. They had reached the Canary Isles before 1336, and their sea power is demonstrated by the conquest of Ceuta in 1415. In 1462 they undertook a voyage to Guinea, visited St. George del Mina in 1481, and some years later JOSEPH VIZINHO accomplished a number of determinations of latitude in Guinea. In 1487—88 BARTHELOMEU DIAZ made his voyage to the Cape of Good Hope, and in 1497 VASCO DE GAMA undertook his expedition to the Indies round the Cape.

In some of their first voyages they probably kept pretty close to the shore, and made use of a few maps, and the compass. But when the voyages became more extended, astronomical determinations became necessary, and it was probably before 1483 that JUAN II, to whom his father had entrusted the administration of the Portuguese colonies in 1474, although he did not succeed to the crown until 1477, called together a Commission or Junta, to examine into