THE DIGITALIZED DOG'S HEART AS AFFECTED BY AMYL NITRITE OR ATROPINE, STUDIED ELECTROCARDIOGRAPHICALLY.

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PLATES 59 TO 65.

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INTRODUCTION.

This investigation was undertaken with the object of determining the action of amyl nitrite and of atropine on auriculoventricular heart block as produced by digitalis or allied substances. In order to do this it was essential first to work out a method of producing this block with a fair degree of regularity, and also to study the effects of amyl nitrite and of atropine on the normal electrocardiogram.

The accomplishment to a satisfactory degree of the first of these prerequisites was prevented by a number of factors. Chief of these was the tendency in normal dogs to sinus arrhythmia, resulting from the constantly changing vagus and sympathetic tone with its consequent sudden and frequent changes in the rate, rhythm, and conduction time, and the fact that in dogs central vagus stimulation often results in sinus inhibition or block, rather than in auriculoventricular block. As all the drugs used in this investigation exert direct or indirect stimulating or depressing actions on both the vagal and sympathetic control of the heart's function, this constantly occurring normal change in the activity of these two mechanisms proved disturbing and must always be considered in the interpretation of the various phenomena observed.

Methods.

The observations are based on thirty-eight experiments in thirty-four animals. In almost all the experiments dogs were used. Three attempts were made to produce auriculoventricular block in cats,
but these were entirely unsuccessful, strophanthin, although slowly and cautiously given, causing none of the usual vagus effects. This failure probably occurred because the cats were restless throughout the experiment, so that the accelerator mechanism from the start maintained complete control of the circulation (Straub (1)).

In the earlier experiments, after taking control curves, light ether anesthesia was induced, a cannula was inserted into the femoral vein, and after waiting until the electrocardiogram appeared to have returned to its original form, the various solutions were injected and curves taken at short intervals. In later experiments the exposure of the vein was made under cocaine-adrenalin anesthesia and no ether was used. This method appeared to possess certain advantages, among which may be mentioned the fact that it was thus possible to avoid the alteration of the normal rate and rhythm of the heart, which ether always causes, and which frequently persisted for an hour or more after cessation of its administration. Control observations showed that in the dosage employed (0.5 to 1 cc. of cocaine, 1:400, and of adrenalin chloride, 1:30,000) these drugs produced no detectable alteration in the electrocardiogram. The blood pressure in a number of experiments was recorded by means of a Harvard membrane manometer inserted into the femoral artery.

In a few experiments, in order to keep the animals still, so that sudden and irregular alterations in the circulation might be avoided, a light but persistent narcosis by the administration of luminal sodium was induced.

In doses of 0.04 to 0.06 gm. per kilo by mouth or subcutaneously this drug usually caused a quiet drowsy or stuporous condition, persisting for 24 hours or longer. At times, however, it caused a marked lowering of the blood pressure and persistent rapid pulse and appeared, in some experiments, to prevent the development of the usual digitalis actions. Its use was, therefore, abandoned. The usual effects of its administration were an increase in the heart rate and an abolition of the sinus arrhythmia which is almost invariably present in the quiet dog. After 36 to 48 hours these effects passed off and the heart returned to its original action. No effects on the electrocardiogram were noted other than were due to the above, which would naturally result from a diminution of the vagus tone, such as is to be expected from large doses of any of the lipoid-soluble narcotics.

1 Straub (1) reports similar results with these animals.
It is important to report that in four of the thirty-four dogs used in these experiments a spontaneous auriculoventricular block was observed. At The Rockefeller Institute for Medical Research in the past 6 years the same phenomenon has been observed in at least four additional cases. The occurrence of this condition, by no means rare, should be remembered by those using these animals, and should lead to caution in interpreting the significance of its appearance. An example of this is seen in Fig. 1, A (Experiment 85).

All observations were made with Lead II. As a majority of the animals survived, control curves were in many instances taken on the following day.

The Effects of Strophanthin and Digitalis on the Normal Dog's Heart.

Strophanthin.

Dosage.—Crystalline strophanthin was injected into the femoral vein in amounts ranging from 20 to 95 per cent of the average lethal dose (1.01 mg. per kilo, according to Jamieson (2)), using a solution of which 1 cc. contained 0.02 mg. of Thoms crystalline g-strophanthin. In the majority of the experiments from 30 to 40 per cent of the lethal dose was injected in about 15 minutes. It was found that the dose which produced a marked vagus effect, as shown by pronounced slowing, auricoul entricular block, or exaggerated sinus arrhythmia, usually lay between 30 and 40 per cent of the lethal dose. Doses above 40 per cent of the lethal dose were likely to produce ectopic ventricular beats or acceleration of the sinus rate, or both. As in many of the experiments the observations extended over periods of several hours and as the various strophanthin effects pass off more reness rapidly, these effects were maintained in a number of experiments by intermittent slow injection of very dilute solutions. The majority of the animals recovered promptly, often within a few hours, from doses up to 60 per cent of the minimum lethal dose.

Rate (Excluding Changes Due to Ectopic Contractions).—In twelve of the nineteen experiments the administration of strophanthin was followed by slowing (Table I, Group A), in four by slowing followed by acceleration (Table I, Group B), and in three by acceleration without previous or subsequent slowing (Table I, Group C).
In interpreting the significance of acceleration of the sinus rate, it is impossible to exclude the influence of psychic factors, but in this series as well as in the digitalis series, reported below, there were a number of instances in which, as far as could be determined by close observation of the dog, the acceleration did not appear to be preceded or accompanied by any evidence of excitement or unrest. The acceleration noted is consequently attributed to a direct action on the sinus node, such as was observed by Rothberger and Winterberg (3) in their experiments on dogs in which the cardiac nerves had been cut.2

Rhythm.—The initial rhythm was affected as follows: auriculoventricular block resulted in nine of nineteen experiments. In one of these (No. 52) it was present in the control curve, was abolished by amyl nitrite, and returned for a short time after strophanthin had been injected. In only two experiments, Nos. 56 (Fig. 2, B) and 57, were fairly persistent auriculoventricular blocks obtained, but in six others occasional blocks were produced.3 In nearly all these cases the sinus arrhythmia was markedly exaggerated by strophanthin. Occasional sinus block was produced in two experiments with interauricular (P-P) intervals ranging up to 1.57 seconds. The sinus arrhythmia was exaggerated by strophanthin in fourteen experiments, but was little or not at all affected in three, and was lessened in two experiments.

Auriculoventricular (P-R) Interval.—This was variously affected by the administration of strophanthin. At some time in the majority of the experiments (fourteen out of nineteen), it was more or less lengthened, on the average by 17 per cent of the initial conduction time. At times this effect was very pronounced, as for example in Experiments 56, 59, and 63, where it was increased from averages of 0.118, 0.112, and 0.116 before, to averages of 0.152, 0.145, and 0.146

2 Under the conditions in my series of experiments a direct stimulation of the central accelerator mechanism may also occur and is not impossible in view of the known stimulation of another closely related sympathetic (the vasomotor) center.

3 In the endeavor to secure the desired auriculoventricular block, the rate of injection, the size of the dose, and the concentration of the solutions injected were varied in different instances, but without success.
### TABLE I.

**Effect of Strophanthin on Sinus Rate in Dogs.**

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<tr>
<th>Group</th>
<th>No. of experiment</th>
<th>Weight (gm.)</th>
<th>Maximum effect on rate (per cent)</th>
<th>Lethal dose given</th>
<th>Duration of administration (min.)</th>
<th>Remarks</th>
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The apparent discrepancy as to frequency of A-V blocks between the table and the text (page 732) is due to the fact that A-V blocks are mentioned under "remarks" only when present at, or near the time when minimum figures occurred.
seconds after the administration of strophanthin. In the three experiments the longest intervals before giving strophanthin were 0.14, 0.14, and 0.13 seconds; after it they were 0.19, 0.165, and 0.21 seconds. In Experiment 62 the longest P-R interval in the control curves was 0.18 second, but after strophanthin there was one of 0.37 second. In two experiments the P-R interval was first lengthened, then shortened; in two others first shortened then lengthened; and in one it was never lengthened, but was slightly shortened from an average of 0.10 to 0.094 second, the sinus rate varying only from 92 to 95 per minute.

In many instances the change in conduction time was obviously influenced by the change in sinus rate, and in many others the changes noted were slight. But there is no doubt that as a general rule the P-R time was lengthened by strophanthin. Pronounced shortening of the conduction time was, however, observed at times in experiments in which it could not be attributed to change in the sinus rate, but would appear to have been due to sympathetic stimulation, either central, from psychic cause, or as a result of direct drug action, or to drug action on the conduction paths themselves. An example of this is Experiment 64 in which the P-R time originally varied from 0.09 to 0.11 second, but after a dose of strophanthin it ranged from 0.10 to 0.17 second, and then after a second dose ranged between 0.07 and 0.10 second, the sinus rate varying only from 80 to 78 to 82 per minute.

P Wave.—In the majority of the experiments (fourteen out of nineteen) the P wave showed no significant changes. In the five others the administration of strophanthin was followed at certain stages by a lessening of the height of this wave, which varied from strongly positive to isoelectric and occasionally became diphasic. In one of these experiments occasional negative P waves were noted. As the height of the P waves varies spontaneously in dogs from time to time and may even be negative in control curves, only a distinct increase or decrease has been considered to be significant. A lessen-

4 For the latter mode of action these experiments produce no evidence, nor is it known to me that an analogous action is exerted by any other drug.

5 The quiet behavior of this dog and the lack of increase in the sinus rate speak strongly against psychic stimulation as a cause of this effect on the P-R time.
ing of its height (Einthoven, and Einthoven and de Waart (4))⁶ or a change to negative appears to result under certain conditions from increased vagus tone, but there are of course other possible explanations for this change in the wave (Rothberger and Winterberg (5)).⁷

_Ventricular Complex (R and T Waves)._—This frequently showed changes (in sixteen out of nineteen experiments). Ectopic ventricular contractions, usually of the left ventricular type, appeared after as little as 19, 25, 30, 31, and 33 per cent of the lethal dose, and almost invariably occurred if more than 40 per cent of the lethal dose was given in about 15 minutes. After the larger doses these ectopic beats were of many types. While nomotopic cycles persisted, the T wave was commonly altered by even smaller doses. Slowing of the sinus rate appeared to exert some influence in favoring the occurrence of ectopic beats, while acceleration appeared to hinder it. In certain experiments large amounts (e.g., Experiment 73, where 70 per cent of the minimum lethal dose was given in 67 minutes) failed to cause ectopic contractions.

As the effective vagus stimulating dose in dogs appears to lie between 20 and 40 per cent of the lethal dose, it is a matter of interest and perhaps of some importance that ectopic ventricular beats are so frequently produced by these doses. In Experiment 56 after 40 per cent of the lethal dose had been given in 13 minutes auriculoventricular block appeared (Fig. 2, B). The ventricular contractions were ectopic in origin, possibly as the result of the stimulation of tertiary centers by strophanthin, which had been previously injected. In all the experiments in which ectopic contractions followed the administration of strophanthin, they appeared during or shortly following its injection, with the exception of certain experiments which will be discussed below, and in which their more tardy appearance can be attributed to the action of amyl nitrite or atropine. In Figs. 3, D, 4 B, D, and E, 5, B, C, D, and E, and 6, G the various types of ectopic complexes noted may be seen.

⁶ This was observed by Einthoven and de Waart (4) after stimulation of the vagus.

⁷ For example, Rothberger and Winterberg (5) obtained negative P waves by simultaneous stimulation of the vagus and accelerator nerves and at times by stimulation of the accelerator alone.
The R wave, as long as nomotopic cycles were present, as a rule underwent no significant alterations in shape. In a few experiments it became much shorter.

The T wave changes were difficult to analyze, as this wave is variable in the normal controls and as it changes rapidly and markedly with changes in rate and rhythm. The change noted by Cohn, Fraser, and Jamieson (6) as characteristic for digitalis in human beings, i.e., a change from one sign to the other, appeared in the majority of the cases where vagus effects (slowing, increase in sinus arrhythmia, etc.) occurred, and was also often present before these effects were apparent. On the other hand, marked vagus effects were at times apparent without the characteristic effect on the T wave. Frequently, especially where there was acceleration of the heart rate with or without the occasional occurrence of ectopic contractions the T wave became decidedly taller (Fig. 7, B), an alteration observed by a number of authors (Selenin (7), Nicolai and Simons (8), Straub (1), and Rothberger and Winterberg, and Einthoven and de Waart (9)), and considered, apparently correctly, by the four last named as the result of a direct stimulation of the sympathetic nerve structures (tertiary centers) in the ventricles.8

Digitalis.

The infrequency with which strophanthin produced persistent auriculoventricular block suggested the use of the entire digitalis body instead of the single active principle. For this reason digipuratum was administered in eleven experiments and a fluid extract of digitalis (Parke, Davis and Company) was used in three others. It is customary in therapeutics, no doubt with justice, to regard strophanthin as more easily absorbed by the heart muscle and its action as more prompt, but at the same time more transitory, than that of digitalis. It was therefore presumed that when digitalis was administered intravenously to dogs, the alteration of rhythm would come on more slowly and more uniformly and would be more

8 In my experiments a direct stimulating effect on the accelerator (or sympathetic) centers may be involved, but Rothberger and Winterberg (9) observed identical changes following the administration of strophanthin in dogs after bilateral vagotomy and destruction of the stellate ganglia.
persistent than had been the case with strophanthin. The use of these bodies was, however, attended by no greater success than when strophanthin was used. Contrary to expectation, the effects produced by digitalis\(^\ast\) ensued as promptly and passed off as rapidly as had been the case with strophanthin. The digitalized heart also reacted to amyl nitrite and to atropine just as did the strophanthinized heart. Apparently in the dog digitalis is rapidly excreted or in some other way rendered inactive. These observations are in accord with the fact that these animals are highly tolerant of digitalis by mouth and with the experience that it has been difficult to produce in them the ordinary digitalis effects by oral administration.

Briefly summarized, the effects usually produced by digitalis or strophanthin under the conditions obtaining in this series were as follows: slowing of the sinus rate, increased conduction time, occasional auriculoventricular blocks, or exaggerated sinus arrhythmia. The T wave in many experiments became negative, but often was unaltered or became more positive.

Ectopic ventricular beats of the left ventricular type frequently followed the administration of doses not exceeding 40 per cent of the minimum lethal dose. Doses larger than this usually caused the occurrence of ectopic ventricular contractions, which at first were of the left ventricular type but later were of various sorts.

The Effects of Amyl Nitrite and of Atropine on the Normal and Digitalized Dog's Heart.

Amyl Nitrite.

Amyl nitrite has been employed clinically (Josué and Godlewski (10), Petzetakis (11), and Belloir and Dubos (12)) as a means of determining whether an auriculoventricular block is due to central vagus stimulation or to direct action on, or organic changes in the conduction paths. Its power of abolishing heart block or of accelerating the sinus rate, according to our present knowledge of its pharmacology, results from its ability to cause a fall of the blood pressure, which in turn depresses the vagus and stimulates the accelerator center.

\(^\ast\)Twelve frog units per kilo were taken as the minimum lethal dose.
Earlier investigators of this drug concluded that it had a marked early stimulation effect on two of the important medullary centers, the vagus and the respiratory, the action on the vagus being attributed by them to reflexes from the upper air passages (Filehne (13) and Brunton (14)). As it has been shown by Pilcher and Sollmann (15) that a third medullary center, the vasomotor, is stimulated even when these reflexes are excluded and as its similar action on the respiratory center is universally recognized, it is possible that the vagus center is also acted on in the same way; i.e., direct stimulation.

The depression of vagus tone which is subsequently seen is due to the fall in blood pressure which amyl nitrite causes and which removes the physiological stimulus for vagus activity. This conception of the cause of the changes in vagus tone during the inhalation of amyl nitrite is in accord with the phenomena observed in this series and accounts for the sequence of events about to be described.

Rate.—In normal, strophanthinized, and digitalized dogs the rate was often slowed at first by amyl nitrite, at times strikingly; as for example in Experiment 53 (Fig. 8, B), in which, after inhalation for 70 seconds, the rate fell from 66 to 42, and Experiment 64 where after inhalation for 20 seconds the rate fell from 72 to 56. This slowing occurred only in dogs in which the vagus was already exerting a marked effect, as evidenced by the slow rate, or auriculo-ventricular block, or sinus arrhythmia. As a rule, with continued inhalation the rate was markedly increased. In Experiment 53, for instance, the rate rose later to 195 per minute (Fig. 8, C).

The primary slowing is undoubtedly due to central vagus stimulation, direct or indirect. It was followed by acceleration, provided

10 Filehne (13), for instance, reports an experiment in which the inhalation of amyl nitrite by a rabbit caused a fall in the heart rate from fifty-three to ten beats per 15 seconds. Pharmacologists have more recently apparently overlooked this early vagus stimulating effect, probably because in ordinary laboratory demonstrations the drug is inhaled through a tracheal cannula. This method, of course, minimizes reflex respiratory effects, while the anesthesia universally employed renders the vagus center less sensitive to stimulation either direct or indirect. I have occasionally seen a primary slowing of the heart rate of slight degree and short duration from amyl nitrite, even in tracheotomized and anesthetized animals. As this investigation was undertaken in the hope of obtaining information bearing on the clinical use of this drug in studying heart block and other arrhythmias, no experiments were done in which the drug was administered by tracheal cannula. Consequently in the majority of the observations made the effects of this vagus stimulation were very apparent.
enough amyl nitrite was given to cause vasodilation sufficient to affect the blood pressure, as was seen in all the observations in which the blood pressure was recorded. The curves show the reciprocal relation between the rise and fall in the blood pressure and the increase or diminution of vagus tone as indicated by the heart rate. These relations may be seen in Fig. 1, B to G. In several experiments where the blood pressure was not recorded even prolonged inhalation of amyl nitrite failed to cause acceleration of the heart rate, but the numerous records where the blood pressure was recorded show no instance where, in spite of a fall in the blood pressure, the heart rate was not accelerated markedly.

**Rhythm.**—As a rule, the rhythm was promptly and decidedly affected by the inhalation of amyl nitrite, sinus arrhythmia or auriculoventricular blocks, whether spontaneous or due to drugs, being (if the drug was given in sufficient doses) abolished or at least markedly lessened (Figs. 1, A, B, D, E, and G, and 8, B and C). In a number of the experiments, however, the effects were preceded by an exaggeration of the arrhythmia due to the vagus stimulation already referred to, and in a number of instances inhalation lasting for several minutes failed completely to abolish the arrhythmia or blocks. An illustration of this early vagus stimulation is seen in Fig. 8, B.

Especially striking was the vagus stimulation in Experiment 53 (Fig. 8, B) in which the interventricular (R–R) interval, which had previously ranged from 0.54 to 1.34 seconds, varied from 0.78 to 4.02 seconds during an inhalation lasting 70 seconds. In this experiment the sinus arrhythmia was not abolished until amyl nitrite had been inhaled for 7 minutes and 40 seconds. In Experiment 64 sinus block (or pronounced sinus arrhythmia) which occurred after strophanthin was given was not abolished by an inhalation lasting 140 seconds, but was abolished later by one lasting 20 seconds. In Experiment 52 a spontaneous auriculoventricular block was not abolished by the first inhalation lasting 60 seconds but was abolished by a second one lasting 90 seconds. In Experiment 56 amyl nitrite inhalation twice failed to abolish an auriculoventricular block due to strophanthin, although the inhalation was continued the second time for as long as 5 minutes. Unfortunately in all the observations cited above the blood pressure was not recorded.

In a number of other experiments in which the blood pressure was recorded, similar but less extreme vagus stimulation occurred, but later gave way to vagus depression (and probably central accelerator stimulation as well) when the vasodilating effect of amyl nitrite became sufficiently pronounced. Fig. 1, A to G
illustrates these effects, both before and after the administration of digitalis to a dog in which there was a spontaneous auriculoventricular block.

In view of the fact that whenever amyl nitrite produced sufficient vasodilation, as seen in the blood pressure records, it also invariably abolished or lessened the arrhythmia or blocks, it may be concluded that its failure to relieve the irregularity in a number of the earlier experiments was due to insufficient dosage.

P-R Interval.—The P-R interval was markedly altered by amyl nitrite. As a rule, the first effect during the stage of vagus stimulation was to lengthen the interval, but later, when a sufficient amount of the drug had been inhaled, the conduction time was markedly lessened, often to 50 to 60 per cent of its original length, while at the same time acceleration of the heart rate took place. These changes are well shown in Experiment 62 in which the P-R time originally varied from 0.09 to 0.16 second. After the inhalation of amyl nitrite for 15 seconds it ranged from 0.11 to 0.56 second, and after 60 seconds was shortened to a uniform length of 0.08 second.

P Wave.—The P wave was frequently markedly altered by amyl nitrite, usually becoming more positive after its inhalation (Figs. 6, B and C, and 7, B, C, and D). In Experiment 62 in which after the administration of strophanthin this wave varied from an isoelectric to a positive form, all P waves became strongly positive during the inhalation of amyl nitrite (Fig. 9, B, C, and D). This change in the P wave corresponds to the change in the form of this wave under the influence of sympathetic stimulation as described by Rothberger and Winterberg (5).

Ventricular Complex.—The ventricular complex, as long as it represented a normally contracting ventricle, often showed significant changes in the T but not in the R wave after amyl nitrite inhalation. The former was frequently altered by amyl nitrite, generally as follows: During the stage of vagus stimulation it often became less positive, but later, as a rule, when the vagus control had been abolished by this drug the T wave became markedly positive (Fig. 7, B, C, and D). When digitalis or strophanthin in not too large amounts had caused the appearance of ectopic beats, amyl nitrite almost always caused their temporary or permanent disappearance (Fig. 4, C). Even after very large doses of strophanthin or
digitalis had caused a constant succession of ectopic beats, the administration of amyl nitrite usually was followed by the reappearance of occasional normal cycles or by striking alteration in the form of the ventricular complexes so that they more closely resembled that of nomotopic ventricular contractions (Fig. 5, C).

In a single experiment (No. 84), in which 33 per cent of the lethal dose of digipuratum had been given 28 minutes earlier, ectopic ventricular contractions appeared for the first time 2 minutes after an inhalation of amyl nitrite, lasting 90 seconds, had abolished a pronounced sinus arrhythmia, and caused a marked acceleration of the sinus rate. The occurrence of these contractions, originating in the tertiary centers, stimulated as they were by the digipuratum previously given, may have been due to the abolition by amyl nitrite of the vagus tone by removing its negative inotropic action on the ventricle alone, or in combination with stimulation of the accelerator center. This explanation seems improbable in view of the fact that the ectopic beats continued to appear from time to time for 26 minutes after the amyl nitrite had been stopped, and that in many other observations amyl nitrite exhibited a striking power of abolishing ectopic contractions if they were already occurring. On the other hand, in no other experiment did ectopic contractions develop so long after the administration of digitalis or strophanthin. Another factor to be considered in estimating the significance of this isolated observation is the occasional, if rare, spontaneous occurrence in dogs of ectopic ventricular contractions.13

In view of the similar reaction of arterial and heart muscle, and of the neuromuscular (intermediate) substance contained therein, to various pharmacological agents (e.g., epinephrin) and physiological stimuli (e.g., stimulation of sympathetic nerve supply), the effects observed in these experiments should have been expected. Because of the close relation of these structures and the known dominant action of amyl nitrite, that is, depression of the sympathetic neuromuscular organs in the arterial walls, it is not surprising that this drug produces a similar depressing action on the cardiac muscle through its neuromuscular (intermediate) substance. It is im-

11 Later in the same experiment, when 44 per cent of the lethal dose of digipuratum had caused almost constant ectopic contractions, inhalation of amyl nitrite for 120 seconds caused them to disappear temporarily.

12 In the series of thirty-eight experiments, this was observed but once, and then in a period when the heart rate was slow, which was not the case in this experiment.
portant to emphasize the fact that, in order to produce this depressing action on the tertiary cardiac centers, very large doses were necessary. Otherwise one might be tempted to expect that one could produce analogous effects in human patients by administering amyl nitrite. That this is possible cannot be denied, but one attempt to do so was unsuccessful.

Atropine.

Atropine also has been used by a large number of clinicians in the study of various types of cardiac irregularity, especially in cases of heart block, to determine whether the block is of vagal or other origin, but as far as is known to the writer it has not been studied experimentally under such conditions as obtain in this series. It is for this reason that it appeared desirable to study its effect on the normal and digitalized heart and to compare its action with that of amyl nitrite.

Atropine sulfate was administered intravenously to twelve dogs in doses ranging from 0.004 to 0.07 mg. per kilo. The effects on rate, rhythm, etc., varied markedly with the size of the dose. Small doses often produced the effects of central vagus stimulation; i.e., lengthening of the auriculoventricular interval and auriculoventricular block. The sinus rate, if affected at all, was accelerated. Larger doses usually produced similar results at the start, but were followed quickly by the effects of vagus depression; namely, acceleration of the rate, shortened P-R interval, and abolition of sinus arrhythmia or of auriculoventricular block.

Sinus Rate.—The sinus rate was increased by atropine in each observation in which any change was noted, but in several experiments the smaller doses produced little or no effect. In no case did the repetition or increase in the size of the dose fail to cause marked acceleration of the sinus rate. The general effect of the action on sinus rate is seen in Table II. In the experiments in which the heart was slowed by previous administration of strophanthin or digitalis the rate after atropinization was increased to approximately

13 This was in a patient with an attack of paroxysmal tachycardia of auricular origin, seen by me through the courtesy of Dr. Lerch in his service at the Charity Hospital in New Orleans.
the same figure as had been reached after similar doses given before strophanthin or digitalis had been administered; that is, the increase in rate was as great after as before digitalization. In the majority of cases, however, the acceleration produced by atropine did not last as long in strophanthinized or digitalized dogs as in the controls.

**Rhythm.**—The effects on rhythm in twenty-four observations varied with the size of the dose. A small dose usually caused auriculo-ventricular block, which was abolished by repetition of the dose (Fig. 10, B and C), or if a block was already present, it was first exaggerated and then abolished. For example, in Experiment 62 administration of strophanthin was followed by marked sinus arrhythmia and occasional auriculoventricular blocks. A first injection of 0.016 mg. of atropine sulfate per kilo caused an increase in the frequency of the blocks, and a second dose of the same size abolished both block and sinus arrhythmia (Fig. 9, E, F, G).

Previous administration of strophanthin or digitalis did not appear to produce either qualitative or quantitative changes in the effects produced by atropine.

**Auriculoventricular (P-R) Interval.**—As was expected, this was markedly affected by atropine. By doses which abolished the arrhythmia or blocks and accelerated the sinus rate it was usually but not always shortened, while after doses causing auriculoventricular blocks it was, as a rule, lengthened. There were, however, many exceptions. Apparently the effect of atropine on the P-R interval was often complicated by the effect which acceleration or retardation of the sinus rate normally exerts in retarding or accelerating the rate of conduction (Table II). As may be seen in a number of instances (Experiments 65, 67, 68, and 69, Table II), and as is illustrated in the chart from Experiment 69 (Text-fig. 1), there is often the same lack of parallelism in the effects on sinus rate and conduction time (P-R interval), to which attention has been called by Cohn and Fraser (16). This may be due either to a quantitatively unequal effect on different parts of the vagus center or on the different vagus nerve endings, the former of which are stimulated while the latter are depressed.
<table>
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<td></td>
<td>+ 0.105-0.12</td>
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<tr>
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<td>42 &quot;</td>
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J. T. HALSEY
P Wave.—In some of the experiments, but not in all, the P wave underwent distinct modifications under the influence of atropine. Usually when atropine caused an auriculoventricular block the P wave became less positive or isoelectric or negative (Figs. 9, F and 10, B). It became positive again when subsequent peripheral vagal depression manifested itself (Figs. 9, G and 10, C). Doses which caused marked acceleration and regular rhythms usually caused the P wave to become more strongly positive.

Ventricular Complex.—The ventricular complex was at times altered in various ways. The T wave during the stage of vagus stimulation showed no changes of significance, perhaps because in all such observations the vagus was already acting rather powerfully before atropine was administered. Later, however, when vagus control had been abolished by atropine, the T wave in most instances became decidedly more positive (compare Fig. 6, E with 6, D). When the ventricular complexes were normal before the administration of atropine, no other changes were noted except in two instances.

In Experiment 64, although large amounts of strophanthin (71 per cent of the minimum lethal dose in 4 hours and 29 minutes, and 77 per cent in 5 hours and 14 minutes) had been given, the ventricular complexes were normal. Two injections of atropine, given 48 minutes apart, were each followed by the occurrence of ectopic beats of the right ventricular type, which persisted each time for less than 10 minutes (Fig. 3, D and E). In Experiment 83, 18½ minutes after 39 per cent of the lethal dose of digipuratum had been given and 60 seconds after a second injection of 0.064 mg. of atropine sulfate incomplete heart block appeared (Fig. 6, F). Ectopic ventricular beats appeared 5½ minutes later (Fig. 6, G). A third injection of 0.125 mg. given 7 minutes later caused their disappearance, but they returned 60 seconds later, then disappeared for a time, but returned from time to time for the next hour. During this period the acceleration of the heart action indicated that the peripheral vagus depressing effect of the atropine was still present.

Whether it is correct to attribute the occurrence of these ectopic contractions to the previously administered strophanthin or digipuratum alone, or to a combination of the action of atropine and the other drug cannot be definitely determined. In favor of the latter explanation are the experiences in two experiments. In Experiment 83, although digipuratum had not been given for a considerable period (24 minutes and 3 minutes) each of the two injections of atropine was followed by ectopic beats, and in Experiment 64 atropine appeared twice to cause their occurrence. The explanation appears to be that the removal of vagus control permits the tertiary centers in the ventricle, already excited by
strophanthin or digipuratum, to inaugurate ventricular contraction. Against this view must be considered the fact that in numerous other experiments under apparently similar conditions atropine did not cause the occurrence of ectopic contractions, but, as will be shown below, appeared at times to prevent them, or to cause their disappearance (Danielopolu (17)).

In a number of experiments, when ectopic contractions appeared after the administration of strophanthin or digitalis, atropine caused them to disappear or to become less frequent (Fig. 4, D, E, and F). At times when large doses of strophanthin or digipuratum had caused a constant succession of ectopic beats, the administration of atropine was followed by a change in the shape of the ventricular complex so that it more closely resembled that of a nomotopic contraction (Fig. 5, D and E), but in other instances under apparently similar conditions this change did not occur. In Experiment 71, for instance, although at an earlier stage atropine caused the discontinuance of ectopic beats, it lost this power later. Both before and after atropine failed, this result was accomplished by giving amyl nitrite. In Experiment 73, after large doses of strophanthin had caused ectopic ventricular contractions, atropine produced about the same effects as did amyl nitrite. Early in the experiment both altered the complex somewhat but later produced little or no effect. A comparison of all the observations made with these two drugs demonstrates the fact that amyl nitrite possesses, to a much higher degree than does atropine, the power of inhibiting or altering ectopic ventricular contractions.

SUMMARY.

The Effects of Strophanthin and of Digitalis.

1. In intact dogs the dose which caused slowing and other signs of vagus stimulation without causing ectopic contractions usually

14Danielopolu (17) reports a case in which the administration of 1.5 mg. of atropine sulfate regularly relieved a bigeminy produced by digitalis or prevented its development even after doses of digitalis larger than those which regularly caused the appearance of bigeminy. In this instance the heart rate was increased markedly (from 70 to 130) by atropine. When the heart became slow again the bigeminy returned. In the experiments under discussion there was no such increase in the heart rate following the administration of atropine.
lay between 30 and 40 per cent of the minimum lethal dose for Thoms
"g-strophanthin"14 and for digipuratum15 and a fluid extract of digi-
talis,16 given intravenously in dilute solution in about 15 minutes.

2. In dogs strophanthin and digitalis when given intravenously
produced typical alterations in the electrocardiogram almost immedi-
ately and with equal rapidity.

3. In this series the changes in the electrocardiogram following
the administration of 25 to 40 per cent of the minimum lethal dose
of strophanthin or digitalis often passed off within an hour or two and
with few exceptions were not visible in electrocardiograms taken
20 hours later. The effects of digitalis did not appear to be more
lasting than those of strophanthin. As there were marked differ-
ences in the persistence of the action of each of these drugs within
its own series, this conclusion is provisional.

4. A persistent auriculoventricular block (without the occurrence
of ectopic beats) was obtained only exceptionally, but the adminis-
tration of 30 to 40 per cent of the minimum lethal dose of either of
these drugs was usually followed by the occurrence either singly
or together of occasional auriculoventricular blocks or exaggerated
sinus arrhythmia or sinus block, and by pronounced slowing of the
sinus rate.

5. Occasionally, with or without previous slowing or the occur-
rence of ectopic beats, these doses caused a marked acceleration of
the sinus rate.

6. The auriculoventricular (P-R) time was usually lengthened
but may be shortened.

7. The P wave may become less positive, isoelectric, or negative.

8. The T wave most often became negative before or during the
stage of slowing but frequently became or remained positive during
this stage. When the sinus rate increased or when occasional ectopic
beats occurred, this wave almost always became decidedly more
positive. At times it varied rapidly and decidedly within a period
of a few seconds.

14 0.12 mg. per kilo.
15 Twelve frog units per kilo.
9. Ectopic ventricular beats occurred in a number of instances after doses ranging from 19 to 40 per cent of the minimum lethal dose, and usually but not always when more than 40 per cent had been injected within 15 to 30 minutes.

10. Previous administration of either of these drugs did not appear to cause either a quantitative or qualitative alteration in the reaction of the heart to amyl nitrite or atropine (with the exception that such previous administration appeared responsible for the fact that in one experiment the inhalation of amyl nitrite, and in two others the injection of atropine, was followed by the occurrence of ectopic beats).

**The Effects of Amyl Nitrite.**

1. In intact dogs, both before and after the administration of strophanthin or of digitalis, the inhalation of amyl nitrite usually caused at first (probably largely reflexly) a pronounced increase of vagus tone shown by slowing of the sinus rate, exaggerated sinus arrhythmia, or auriculoventricular block. Later the sinus rate was accelerated and arrhythmia or blocks disappeared (probably due to vasodilatation and diminished vagus tone).

2. The auriculoventricular (P-R) time was usually lengthened at first and later was shortened.

3. The P wave often at first became shorter, isoelectric, or negative, but later became much more positive.

4. The T wave at first often became less positive or more negative, but later became strongly positive.

5. When the previous administration of not too large doses of strophanthin or digitalis caused the occurrence of ectopic ventricular beats, the inhalation of amyl nitrite usually caused their temporary disappearance. Even when large doses of these drugs caused a constant succession of ectopic contractions of various types, its inhalation was often followed by a temporary return of nomotopic cycles or by a change in the form of the ventricular complexes so that they more closely resembled that of nomotopic ones.

6. Only large amounts of amyl nitrite appear to have the power to prevent ectopic ventricular beats or to alter their type.
The Effects of Atropine.

1. In intact dogs before and after the administration of strophanthin or digitalis, small doses of atropine usually caused auriculo-ventricular block (or exaggerated it if already present). Larger doses, after first producing the same effect as the small ones, caused an increased sinus rate and abolished blocks or sinus arrhythmias if present.

2. The P-R time was usually lengthened by small doses and shortened by larger ones.

3. The P wave sometimes became shorter at first (less positive), isoelectric, or negative, but later (when the peripheral vagus paralysis ensued) it became positive again, often much more so than it was originally.

4. When ectopic contractions were present as a result of previous administration of strophanthin or digitalis, atropine, like amyl nitrite, often caused their disappearance, or altered the form of the ventricular complex, but was less efficient in this direction than amyl nitrite.

5. Occasionally the injection of atropine into dogs, which had previously received strophanthin or digitalis, appeared to facilitate or bring on the occurrence of ectopic ventricular contractions.

I wish to acknowledge my indebtedness to Dr. Alfred E. Cohn for his courtesy and assistance during the experiments and in the preparation of the manuscript.

BIBLIOGRAPHY.

J. T. HALSEY


EXPLANATION OF PLATES.

In all the figures (except Fig. 9, A to G) divisions of the abscissae equal 0.04 second. In Fig. 9, A to G the time is indicated by the lowest line, each interval representing 0.2 second. Divisions of the ordinates equal $10^{-4}$ millivolts. In Fig. 1, B to G the upper curve represents the blood pressure as recorded by a Harvard membrane manometer, a rise in the curve denoting a fall in the blood pressure. All the curves were made with Lead II (right fore leg to left hind leg).

PLATE 59.

Fig. 1, A to G (Experiment 85). In the upper curve, which is that of the blood pressure, a rise of the curve indicates a fall in the blood pressure.

A and B are controls. In A there is a spontaneous auriculoventricular block.

C was taken when amyl nitrite had been inhaled for 90 seconds. The blood pressure has fallen and as a consequence the heart beats more rapidly than in the control until this increase in heart rate leads to a rise in blood pressure which is followed by an auriculoventricular block. The P waves have become much taller than in the control curves.

D was taken 60 seconds after C when the inhalation had lasted 2½ minutes. The blood pressure has fallen in spite of the increased heart rate, and blocks and sinus arrhythmia have been abolished.

E was taken 1 minute after 29 per cent of the minimum lethal dose of a fluid extract of digitalis had been injected in 72 minutes. It shows an auriculoventricular block and a sinus arrhythmia.

F was taken 4 minutes after E when amyl nitrite had been administered for 3½ minutes. The sinus rate has increased and the blood pressure has fallen decidedly, but the curve shows one auriculoventricular block and some sinus arrhythmia.

G was taken 30 seconds after F when the inhalation had lasted 3½ minutes. The blood pressure has fallen still further, and arrhythmia and blocks are abolished. The sinus rate is markedly accelerated, the P–R interval is shorter, the P waves are much taller, and the T waves are more positive than in E.
FIG. 2, A and B (Experiment 56).
A is the control.
B shows auriculoventricular block with ectopic ventricular beats developing 6 minutes after the injection of 40 per cent of the minimum lethal dose of strophanthin. It also shows a negative T wave and the P-R interval increased to 0.17 second.

FIG. 3, A to E (Experiment 64).
A is the control. B and C serve also as controls to D and E.
B was taken when 71 per cent of the minimum lethal dose of strophanthin had been administered in 4 hours and 29 minutes. It shows slowing of the sinus rate and marked sinus arrhythmia with negative T waves.
C was taken 4 minutes and 20 seconds after B, and 80 seconds after the injection of 0.19 mg. of atropine sulfate. It shows abolition of sinus arrhythmia and marked acceleration of sinus rate, increase in height of the P waves, and change in form of the T waves. The P-R interval is almost unaltered.
D, taken 2 minutes and 50 seconds after C, shows ectopic ventricular beats.
E, taken 3 minutes after D, shows ectopic ventricular beats.

FIG. 4, A to F (Experiment 71).
A is the control.
B was taken after 44 per cent of the minimum lethal dose of strophanthin had been injected in 23 minutes. It shows ectopic ventricular beats.
C was taken 80 seconds after B. Amyl nitrite has been inhaled for 40 seconds. It shows the disappearance of ectopic beats.
D was taken 8 minutes after C. It shows a return of the rhythm seen in B. No additional strophanthin has been given.
E was taken 16 minutes after D; 5½ minutes after 50 per cent strophanthin had been injected in 43 minutes; 15 minutes after a first injection of atropine sulfate, 0.0125 per kilo; and 2 minutes after a second injection of the same size. It shows the altered form of the ventricular complex.
F was taken 3 minutes after E and 30 seconds after the injection of a third dose of atropine sulfate, 0.025 mg. per kilo (0.05 mg. per kilo in all). It shows normal cycles.

FIG. 5, A to E (Experiment 73).
A is the control.
B was taken 6 minutes after the injection of 96 per cent of the minimum lethal dose of strophanthin in 1 hour and 47 minutes. It shows ectopic ventricular beats of different types.
C was taken 90 seconds after B, when amyl nitrite had been inhaled for 60 seconds. It shows alteration in the form of the ventricular complexes.
D was taken 90 seconds after C. No amyl nitrite was given for 90 seconds. It shows the return to curves similar to those in B before inhalation of amyl nitrite.

E was taken 3 minutes after D, 30 seconds after the injection of atropine sulfate, 0.07 mg. per kilo. It shows ventricular complexes like those seen in C, following the inhalation of amyl nitrite.

PLATE 62.

FIG. 6, A to G (Experiment 83).
A is the control.
B was taken 4 minutes after 37 per cent of the minimum lethal dose of digipuratum had been injected in 2 hours and 25 minutes. It shows slowing of the rate with sinus arrhythmia.
C was taken 2 minutes after B. Amyl nitrite had been inhaled for 60 seconds. The curve shows abolition of sinus arrhythmia, acceleration of sinus rate, increase in height of P waves, and strongly positive T waves.
D was taken 19 minutes after C, 15 minutes after 39 per cent of the minimum lethal dose of digipuratum had been injected during 2 hours and 46 minutes.
E was taken 90 seconds after D and 30 seconds after the injection of atropine sulfate, 0.012 mg. per kilo. It shows slight variation in the height of the P waves and a marked change in the T waves which are much more positive than in D.
F was taken 2 minutes after E, 60 seconds after a second dose of atropine sulfate, 0.012 mg. per kilo. It shows three auriculoventricular blocks and further change in the T waves.
G was taken 5½ minutes after F. It shows ectopic ventricular contractions, alternating with cycles like those in F.

PLATE 63.

FIG. 7, A to D (Experiment 83).
A is the control.
B was taken 10 minutes after the injection of 20 per cent of the minimum lethal dose of digipuratum in 34 minutes. It shows ectopic beat and an auriculoventricular block, also tall T waves. The P-R interval is increased.
C was taken 4 minutes after B when amyl nitrite had been inhaled for 20 seconds. It shows an ectopic beat and an auriculoventricular block. The T wave has become less positive.
D was taken 20 seconds after C when amyl nitrite had been inhaled for 40 seconds. The sinus rate accelerated, the P-R interval shortened, and the T wave became strongly positive. The P waves are now all very tall.

FIG. 8, A, B, and C (Experiment 53).
A is the control.
B was taken 70 seconds after the commencement of inhalation of amyl nitrite. It shows an R-R interval of 4.02 seconds.
C was taken at the end of the inhalation, lasting 7 minutes and 40 seconds. It shows a greatly increased rate and regular rhythm. The P-R interval shortened to 0.08 second.

**Plate 64.**

**Fig. 9, A to G (Experiment 62).**

A is the control.

B was taken immediately after the injection of 19 per cent of the minimum lethal dose of strophanthin. It shows an auriculoventricular block, an ectopic ventricular beat, a change to a negative T wave, and a slightly lengthened P-R interval.

C was taken 2 hours and 10 minutes after B. 36 per cent of the minimum lethal dose had been injected in 3 hours and 15 minutes. It shows exaggerated sinus arrhythmia, P waves varying from strongly positive to isoelectric, and negative T waves.

D was taken 4 minutes later; amyl nitrite had been inhaled for 30 seconds. The arrhythmia is abolished, the rate markedly increased, the P-R time shortened to 0.08 second, all P waves are strongly positive, and T waves changed from negative to diphasic.

E was taken 23 minutes and 20 seconds after D. 40 per cent of the minimum lethal dose of strophanthin has been injected in 3 hours and 42 minutes. It shows marked sinus arrhythmia, one blocked P wave, P waves varying from strongly positive to isoelectric, and T waves of variable degrees of inversion.

F was taken 3½ minutes after E and 2 minutes after the injection of 0.016 mg. of atropine sulfate per kilo. It shows much more frequent auriculoventricular blocks, P waves of varying heights, and a lessening in the negativity of the T waves.

G was taken 12½ minutes after F and 5 minutes after the second injection of 0.016 mg. of atropine sulfate per kilo. It shows marked acceleration of sinus rate, abolition of block, and almost complete merging of T and P waves, both of which are strongly positive.

**Plate 65.**

**Fig. 10, A, B, and C (Experiment 68).**

A is the control.

B was taken 30 seconds after the injection of atropine sulfate, 0.006 mg. per kilo. It shows an auriculoventricular block with negative P waves. It also shows P waves changing from negative to positive and back again to negative.

C was taken 7 minutes after B, and 35 seconds after the second injection of atropine sulfate, 0.006 mg. per kilo. It shows accelerated sinus rate, abolition of block and arrhythmia, shortened P-R interval, the P waves strongly positive, and change of the T wave to strongly positive.
(Halsey: Digitalized Dog's Heart.)
(Halsey: Digitized Dog's Heart.)
(Halsey: Digitalized Dog's Heart.)