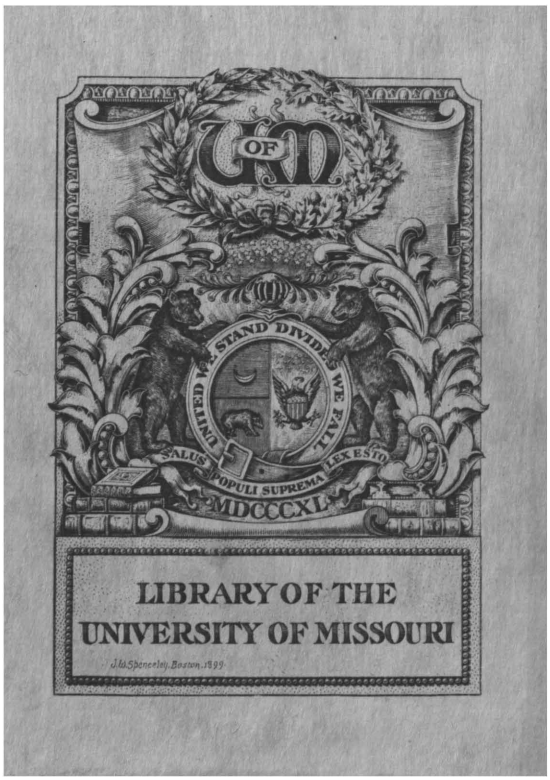

THE PHARMACOLOGICAL ACTION

OF

ACETANILIDE, ANTIPYRINE AND ACETPHENETIDIN

ON CARDIAC MUSCLE.

by

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Introduction.

It is a well known fact that acetanilide and the antipyrine series, when administered in clinical cases, for antipyretic purposes, often have untoward and unexpected accompanying actions. These associated influences have not yet been fully inquired into by experimental methods. There has grown up a consensus of opinion, based on general evidence, that the circulatory system, especially the heart is impaired and that the oxygen carrying power of the blood cells is lessened because of a chemical change.

It is the purpose of this paper to present the results of a series of experiments on the action of these drugs on isolated cardiac muscle, both on tissue known to contain nerve ganglia, the sinus; and on that free from nerve ganglia, the apex strip of the ventricle.

Review of the Literature

a, The Chemical Nature of the Drugs; Acetanilide, Antipyrine and Acetphenetidin.

In the destructive distillation of coal, by heating in a closed retort for the production of illuminating gas, there are produced several gases, the residual coke and the intermediary tar (I). From the latter are derived a great variety of products consisting of several volatile liquids, principally benzene or benzol, toluene or tuluol, the so called aromatic alcohols, phenol, cresol and a graet variety of bases of the ammonia type, including anilin and solid naphthalin. Acetanilide and the antipyrine series; antipyrine and acetphenedin, drugs recently introduced into therapeutics, the oldest being known only since 1884, are derivaties from these intermediary tar products.

Antipyrine, ($C_6H_5-N<^{N(CH_3)-C(CH_3)}_{CO-CH}$), is derived from the interaction of acid with phenylhydrazine, ($C_6H_5NH-NH_2$) Anilin with acetic acid produces a colorless compound, a crystallized salt which is acetanilide, ($C_6H_5-NHCOCH_3$). Anilin is found only in small quantities in coal tar so that it was not until it was produced artificially did it become important. A synthetic compound was made by the action of nitric acid on benzene. The benzene molecule is changed into nitro benzene, ($C_6H_5-NO_2$). When subjected to nascent hydrogen, the nitrobenzene is changed into anilin, phenylamin or amidobenzene, ($C_6H_5NH_2$), an oily liquid of strong basic properties and which forms crystallizable salts with acids. When it was found that acetanilide underwent a partial oxidation in the body with the formation of amidophenol or its derivaties, and since there was a belief that the antipyretic effects were not so much due to the original substance as to these oxidation products, the numerous derivaties of paramidophenol,

($C_6H_4(OH)NH_2$) were introduced (2). The first of these was acetphenetidin, ($C_6H_4(NHCOCH_3)OC_2H_5$)

b, The Pharmacological Action of the Coal Tar Drugs.

There are only scattering references here and there in the literature as to the specific action of these coal tar derived drugs on the circulatory system.

Sollmann(3) states that members of this group first accelerate and then slow the heart. since there is conceded to be a difference in the toxicity of these three drugs I shall consider them separately and in the order of their relative toxicity; viz. acetanilide, antipyrine and acetphenetidin.

Acetanilide.

Potter(4) says that acetanilide depresses the heart. Butler(5) says that toxic doses cause great cardiac depression by direct action on the heart. In medicinal doses ,however, the arterial tension is slightly raised, though the heart is slowed. Mc Farlane (6) speaks of the depressant effect of the drug upon the heart. In clinical cases reported in the Journal of the American Medical Association, it is stated that there is manifest a loss of cardiac tone and a feeble heart accompanied by a small, soft and almost imperceptible pulse (7 & 8). One of the earliest reports in the history of the drug, of the adverse action of acetanilide on the circulatory system is made by Faust(9). He states that in man antifebrin, acetanilide, makes the heart become very weak, causes a decrease in pulse rate and a rise in arterial pressure. Experiments made on the action of acetanilide on the frog's heart, the perfusion method being used, led Worth Hale(Io) to state that acetanilide is markedly depressant,

producing a very slow heart rate and decreasing even more definitely the amount of fluid pumped through the heart. This investigation was continued on mammals. It was found that this drug slowed the mammalian heart. Since paralysis of the vagi had no effect on this action, the slowing was evidently due to a direct action on the heart muscle. Another testimony is added to this observation that the drug is depressing, by Probasco(II), who says that it depresses the heart even in small doses by direct action on cardiac muscle. A slight exception to the foregoing concurrence of observations is the statement of A.Bokai (I2); that acetanilide works only a minimum amount upon the heart.

Antipyrine.

Antipyrine is not without effect upon the human heart(I3) according to investigations made with the sphygmomanometer and the sphygmograph. It was found that there was an increase in the wall tension and the blood pressure as a sequel, following the administration of this drug. There was also noticed an increase then a lowering of the irritability of the heart.

Experiments made upon the rabbit and the frog, poisoned by antipyrine, showed a lessened blood pressure following the initial increase. After comparatively small doses of this drug the amplitude of the contractions of the frog's heart was moderately uneven.

A histological study was by Iwanoff of the liver of rabbits,following and without the administration of antipyrine. Comparisons were made between the relationship of the volume of the blood vessels and the surrounding liver cells in each case. The results were that without exception the blood vessels of the drugged specimens were very expanded when compared with the control specimens.

Breitenstein(I4) found that there was always a change in the pulse frequency following the use of antipyrine. There never was an increase, and the fall in rate was from 0 to 22 beats per minute. The blood pressure was practically unaffected. Other investigators found that following the administration of the drug to mammals the strength of the beat was somewhat lowered and the number of the beats increased from 2o to 4o beats per minute. Since section of the vagi increased the number of beats but very slightly the effect might have been due to direct action on the heart muscle. Cardiac depression, marked palpitation and disturbances of the heart's rhythm are not uncommon symptomsof antipyrine poisoning(I6, I7). These resulting symptoms may be referred partially to changes in the vasomotor system, but the toxic effects upon the cardiac muscle can not be excluded.

An interesting and suggestive observation the effect of this drug on a closely allied tissue, the striated muscle of the frog's gastrocnemius, showed that the period of contraction was very much prolonged in the poisoned muscle over the normal one.

Acetphenetidin.

Acetphenetidin, the mildest of the antipyretic coal tar drugs, is credited by some with having no influence on the heart action(I8). Mahnert(I9) asserts , however, that this drug is capable of producing degradation of the heart muscle, be it after one large or often repearted small doses. It also causes a change in the caliber of the arteries, bringing about weakness and collapse as a sequel. Hirschfelder(2o) observed arythmia of the pulse allied with interruptions of the heart beat, after the administration of this drug.

Summary of the Literature on the Action of Acetanilide, Antipyrine and Acetphenetidin on the Heart.

Acetanilide is a more toxic drug than antipyrine, and the latter more toxic than acetphenetidin.

Acetanilide is conceded by the majority of investigators to be a cardiac depressant, the action being directly upon the muscle . Prevention of complete relaxation of the muscle has been noticed.

Antipyrine acting directly on the cardiac muscle while usually depressant may exhibit an initial stimulating influence at times, followed by the depressant effect. Excessive relaxation has been found as a sequel.

Acetphenetidin has been observed to cause irregularities of the rhythm of the heart, and to cause injury to the cardiac muscle.

Review of the Literature on the Structural Characteristics of the Tissues Used.

Cardiac Muscular Structure.

It may be well to consider in advance some characteristics of the cardiac tissues, the sinus and the ventricle, that were used in this experiment.

It is generally thought that there are structural differences in the muscle fibers of these two regions of the heart in addition to the difference in innervation. The sinus structurally, is more like the veins into which its tissues merge and its fibers bear similiarity to smooth muscle fibers , while the ventricular muscle is more like the striated skeletal muscle. Gaskell(2I) states, however, that," The muscle fibers through-out the heart are of the same type. Any differences that are seen are differences in the prominence of the various structural peculiarties of the cardiac type of muscle, and are not so great as the differences between striated and unstriated muscle fibers". " T hus all muscle fibers are to a greater or less extent transversly striated, but the prominence of the striations varies considerably. Similarly the thickness of the fiber, the extent of parallelism of its edge, the relative size of the nucleus to the size of the fiber all present differences in different parts of the heart". The greatest constrast is seen when single fibers of the sinus are compared with those of the ventricle. The sinus muscle fiber is more delicate and tapering, and shows a striation that is decidedly indistinct. The ventricular muscle fiber is thick and boldly striated.

The Innervation of Cardiac Muscle.

Keith and Flack(22) found similar tissue near the sino-auricular junction in the turtle's heart to that in the mammalian heart which is called the Keith and Flack node. By microscopic examination of the tissues they showed the presence of nerve cells.

It is generally conceded by investigators that the lower half of the ventricle, the apex, contains no nerve cells. Gaskell(2I) found no nerve cells in this part of the ventricular muscle. Berkley and later Carlson have described single nerve cells in the ventricle but no ganglia have been shown. Mr. Stowers working in the Physiological Laboratory of the University of Missouri, found no evidences of nerve cells in this part of the ventricle.

Functional Characteristics of Cardiac Muscle.

Cardiac muscle has rhythmic action most highly developed, rapidity of action and tonicity are well marked(2I). The property of inherent highly developed rhythmicity of cardiac muscle and its relative rapidity of action is well known. The characteristics of tone which the muscle exhibits continuously is not so well understood. Since the action of these drugs,-acetanilide, antipyrine and acetphenetidin, is shown very evidently in respect to tone of the muscle , an inquiry as to its mechanism is desirable.

Fano(23) , one of the earliest investigators to make a special study of this property of muscle tone, suggested that the tone changes and contractions may be due to the activity of a substance in the heartv muscle different from that which mediates ordinary contractions. Botazzi(24) suggests that while the fundamental contraction is due to the cross-striated substance, the slower tone changes may be due to undifferentiated sarcoplasm.

The idea that tone is produced by a state of partial and continuous activity of all the muscle fibers is not in harmony with what is known of normal physiological processes in muscles and in other tissues, and it postulates a peculiar form of activity differing in certain respects from common modes of acting(25).

Lingle(25) concluded from experimental data that tone is produced by the same form of activity that is shown by muscle cells in ordinary forms of contraction. It is attended by fatigue of the elements involved, but shows a uniformity of action because only a part of the tissue is involved at one time. When one element or a certain number of fibers is fatigued a resting one or a relay takes its place. Tone rhythms are produced by an imperfect correlation between active parts.

Observations made on the tonus of heart muscle by Porter(26), are in harmony with the theory of Lingle's stated above. He found that the conductivity for the fundamental contractions lessened as the tone increased. This is to be expected if we concede that the morphological units involved in tone are the same, as to kind, as those which cause fundamental contraction, and that the greater the tone, the greater the number of units involved. The slower conductivity during great increase in tone may be explained by the fatigue of the greater number of units involved in the tone contraction. His investigation also indicated to him that the tonus contractions have no refractory period, extra contractions may be produced during any phase of the tone contractions, and the height of the contraction is in proportion to the strength of the stimulus. If we accept the"all or none"theory of the contraction of cardiac muscle and also the theory of the division of labor of parts of the muscle fiber, i.e. the

production of tone by the activity of the sarcoplasm or some other substance different from that which mediates the ordinary contractions, the production of extra superimposed tone contractions would be impossible and the proportionate relationship between the height of the contractions would be unlookt for.

Summary of the Literature on the Structural and Functional Characteristics of Cardiac Tissue.

Muscle fibers through-out the heart are of the same type, they differ in the prominence of various structural characteristics.

The sinus contains nerve ganglia. The apex strip of the ventricle is probably free from nerve ganglia.

Cardiac muscle has rhythmic action highly developed. Rapidity of action and tonicity are well marked.

Experimantal evidence supports Lingle's theory of tone rather than the theory of the mediation of tone by the sarcoplasm.

Experimental Methods.

a, Turtles used.

The turtles that were used were for the most part Chrysemus Emyd Blandingii.

b, Preparation of the Strips.

The preparation and mounting of the ventricular strips was done as directed in Greene's Experimental Pharmacology. They were made to contract against a tension of one gram in addition to the weight of the light lever. The magnification of the contractions was 7.2 in one series , and in the other series 7.6 . Rhythmic contractions began after a latent period of Io to 9o minutes after being mounted.

The sinus strip included beside the sinus, about fifteen millimeters of the left vena cava. One ligature was first placed around the left cava, a second was placed beneath the posterior vena cava and tied. The strip was then removed from the attached auricles and vein and mounted in the same manner as the ventricular strip. Because of its delicacy, the sinus strip was made to contract against a slight tension , that of the weight of the light lever only. The magnification of the contractions was 6.3 times. Tone waves were exhibit when the strip was first mounted. There was often a latent period for the fundamental contractions if they were developed at all.

c, Solutions.

In the first few experiments a solution of .7 percent sodium chloride was used for the normal solution and as a vehicle for the drug. It was found that this solution brought about early exhaustion of the strip. Greene(27)

found that after a short period, twenty minutes, of regular contraction of the ventricular strip in .7 percent sodium chloride, there was a gradual and uniform decrease in amplitude simulating exhaustion. If Ringer's solution (NaCl .7%, KCl .03%, CaCl .026% ,) were used on this seemingly exhausted strip, strong and regular contractions occured. Consequently the use of a combination of the two solutions making a weakened Ringer's solution was suggested. The solution used contains NaCl .7 percent, KCl .01 percent and CaCl .0086 percent . This weakened Ringer's solution seemed highly satisfactory in that it sustained the strip in rhythmic contractions and at the same time prevented the appearance of exhaustion.

The tubes of the bathing solutions, as a rule were shaken up vigorously in air to get as much oxygen as possible into solution before it was used.

The strips were rinsed after the removal of the drug solution before immersion into the normal solution.

The Action of Acetanilide on Contracting Ventricular Strips.

Upon the application of solutions of .oI to .o5 percents of acetanilide to contracting ventricular strips there is always some change in their activity. The change is one manifest by a stimulating effect rather than a depressing one, (see tables I--5). This stimulating action may be evident in both amplitude and rate as is shown in the following experiments; Exp.5o,trial I, table 3 ; Exp.5I, trials I&2, table4; exp.52, trial I, table4; exp.46, trial3, table5; It occurs when acetanilide is used in.o5, .o4, .o3 , percent solutions. In one experiment , exp.49, trialI, table 2, .o2 percent is used with the same result, i.e. a stimulation shown in both amplitude and rate.

In other experiments the stimulating effect is shown either in the amplitude or the rhythm but not in both. This is the rule in the experiments of the first two tables. In most cases when weaker solutions are used, .oI and .o2 percents, the stimulating effect is shown more in the later part of the experiment than in the first part, the effect being nearer like that produced by the the three stronger solutions mentioned above. This suggests that the drug is cumulative in its action, but what is more probable is that the longer the experiment is continued the more of the strip is affected by the transfusion of the drug into the tissue. This latter supposition is supported by the fact that not even a semblance of a cumulative effect is shown from one trial to another in an experiment on the same strip.

There seems to be justification for the statement that the weaker percents of this drug; .o5, .o4, .o3 , afford maximum stimulation to ventricular strips. Solutions weaker than these stimulate, but in varying less degrees.

Tables I -- V show the effect of different strengths of acetanilide on the amplitude and the rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of the normal.

Table I

Exp. No.	Trial No.	Duration of exp. in min.	Per cent of drug	Amplitude and rate stated as percents of the normals, after a given number of minutes. Time, Amp, Rate—Time, Amp, Rate.					Notes
48	I	38	.oI	I.5	Io2	Ioo	-- I5	87	Ioo	
47	I	35	.oI	"	Io5	Ioo	-- Io	III	Ioo	

Table II

49	I	2o	.o2	"	Ioo	I33	-- I5	Io6	I33	
49	2	II	.o2	"	Ioo	II2	-- Io	Ioo	II2	
49	3	Io.5	.o2	"	98	85	-- 5	Ioo	83	Slight irregularities in rhythm.
49	4	I9.5	.o2	"	94	IoI	-- I5	98	I25	

Table III

5o	I	Io.5	.o3	"	IIo	I38	-- 5	IIo	III	
5o	2	8	.o3	"	Io7	Ioo	-- 5	II3	Ioo	Slight irregularities both in amplitude and rate occured during and after this experiment.

Tables I —V showing the effects of different strengths of acetanilide on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of the normal.

Table IV

Exp. No.	Trial No.	Duration of exp. in mins.	Per-cent of drug	Amplitude and rate stated as percents of the normals, after a given number of minutes						Notes
				Time,	Amp.	Rate	Time,	Amp,	Rate.	
5I	I	8.5	.04	I.5	Io7	II2	8	III	II2	A few irregularities in rhythm occured.
5I	2	8.5	.04	"	Io7	Io7	6	Io7	II5	Slight irregularities in both amplitude and rate.
52	I	I8.5	.04	"	IIo	III	5	IIo	I4o	Irregularities in rate in the third minute.

Table V

45	I	Io.	.05	"	II2	Ioo	5	I35	85	Normal amplitude and rate recovered three minutes after the removal of the drug.
46	I	26	.05	"	Io4	Ioo	5	IIo	86	
46	2	25	.05	"	Ioo	I2o	7	94	I3I	
46	3	I4	.05	"	Io7	II4	4	94	Ioo	

Table VI contains data on the effects of a stronger solution, .I percent, acetanilide on the contracting ventricular strip. This concentration produces a stimulating effect. The stimulation may appear in either amplitude or rate with no change , or with an accompanying and approximately compensating decrease in the other. If the experiment lasts no longer than nine minutes , there is always an increase stimulation as the experimant proceeds, as shown in exp.34, trial 2, table 6; exp. 4o, trial I&2, table 6; exp.42, trial I, table6; On the other hand, if the experiment lasts ten minutes or longer, there is depression. This is shown in exp. 34, trialI, table 6; exp. 42, trial2, table 6.

A .I2 percent solution of acetanilide has a stimulating effect manifest as a rule in either the amplitude or the rate. Occasionally there is an increase shown in both amplitude and rate as may be seen in exp.3I,trials I&2, table 7; exp. 3o, trials 3&5, table 7; In other cases the increase in the one factor is accompanied by a decrease or no change at all in the other . The depressing effect as the experiment proceeds is evident in 85 percent of the experiments. In Io percent of the experiments there is no change from the initial effect. In all the experiments it is evident that the longer the application of the drug the greater the greater is the depression.

An interesting fact is shown in exp. 3I,trials I3,I4& I5, table 7. After being mounted for 38 hours following the first I2 trials, the strip is greatly depressed upon the application of acetanilide; there is no initial increase as usual,instead there is complete quiesence after one minute of the following, the thirteenth, trial and great slowing in the fourteenth and fifteenth trials.

This suggests that the stimulating or depressing actions of a certain strength of a drug solution is dependent on the vitality of the cardiac tissue used.

It seems evident that there is only a slight difference in the percentages of the drug that stimulate and those that depress the contracting heart strips.

Table VI showing the effects of .I percent acetanilide on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

I2/6/Io

Exp. No.	Trial No.	Duration of exp. in mins.	Per cent drug	Amplitude and rate stated as percents of the normals, after a given number of minutes. Time, Amp. Rate			--	Time, Amp. Rate.			Notes
34	I	Io.5	.I	I.5	Ioo	Io5	--	Io	8o	III	Very slight irregularity occurs in amplitude.
34	2	8.5	.I	"	98	Io7	--	7	86	I25	Slight irregularities in both amplitude and rate.
2/6/II											
4o	I	9.4	.I	"	Io3	83	--	6	94	II3	
4o	2	II.5	.I	"	Io2	Ioo	--	9	II2	95	
2/8/II											
42	I	Io.	.I	"	Io7	87	--	8.5	II4	98	
42	2	I6	.I	"	Ioo	Io7	--	I5	7I	Ioo.	

Table VII showing the effects of .I2 percent acetanilide on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution . The results are figured as percents of normal.

Exp No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate stated as percents of the normals, after a given number of minutes. Time,	Amp.	Rate,	-- Time,	Amp.	Rate.	Notes
3I	I	3.3	.I2	I	IoI	I25	--	3	Io4	75	A few incomplete relaxations oscured just after the drug was removed.
3I	2	4.2	.I2	"	Io3	II2	--	3	Io5	75	Incomplete relaxations occured during the bath.
3I	3	Io	.I2	"	Io3	75	--	9	9o	I5o	Rhythm slowed just after the bath.
3I	4	6	.I2	"	99.5	II6	--	5	IoI	II9	
3I	5	I3	.I2	"	Ioo	Ioo	--	I3	93	9I.5	
3I	I2	7	.I2	"	Io4	Ioo	--	7	94	Io2	
3I	I3	5	.I2	"	IIo.5	66	--	0	o	o	Contractions stopped after the first minute.
3I	I4	I2	.I2	"	Io9	42					Only periodic contractions, I per minute occured through the remainder of the experiment.
3I	I5	2.5	.I2	"	II3	83					The rhythm ceased after two contractions in this experiment.

The last three experiments above were made after the strip had remained in Ringer's solution over night, had failed to give a constant amplitude and rate the second day and had remained in Ringer's solution the second night.

Table VII showing the effects of .I2 percent acetanilide on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Per-cent of drug	Amplitude and rate stated as percents of the normals, after a given number of minutes. Time,	Amp.	Rate	-- Time,	Amp.	Rate.	Notes.
3o	I	6	.I2	I	77	IIo	-- 2	Ioo	Ioo	
3o	2	3.2	.I2	"	III	I0o	-- 3	Io7	Ioo	Slight arrhythmia
3o	3	4.75	.I2	"	IIo	I2o	-- 2	Io6	Ioo	
3o	4	7	.I2	"	97	I28	-- 4	Io4	96	
3o	5	9.5	.I2	"	Io4	II8	-- 3	III	9o	
3o				Same			-- 7	82	44	
32	I	Io.5	.I2	"	Io4	86	-- 4	III	69	Irregularities of rhythm occured.
32	2	6	.I2	"	96	97	-- 3	98	84	
32	3	5	.I2	"	Io8	8o	-- 4	Io5	73	
32	4	5	.I2	"	Ioo	Ioo	-- 4	56	I6o	
33	I	5.5	.I2	"	Io9	Ioo	-- 5	I26	26	Quiesence during the fourth minute, then a very slow rhythm followed.
33	2	7	.I2	"	Io5	Ioo	-- 6	Io5	94	
33	3	I2.5	.I2	"	Io6	84	-- I2	IoI	54	

Note. A control strip taken from the same heart and subjected to the same treatment as the drugged strip showed, at the end of the experiment, an amplitude, I62 percent of normal, and a rate 75 percent of normal.

The drugged strip showed , at the end of the experiment, an amplitude of 114 percent of the original normal , taken before the series of trials began. The rate was 35 percent of the original normal.

As is usual upon the application of this drug, acetanilide, there is a change in the amplitude and the rate of the strip when bathed in a .I5 percent solution,(see table 8). In 86 percents of the cases in which .I5 percent solution of acetanilide is applied to the strip there is absolute increase in the work,or efficiency, of the same. The increase comes predominately upon the amplitude. In 5o percent of the trials the rate either remains the same or is depressed.

The results of increasing percentages of the drug are consistent in one respect. They show that depression is the characteristic action of acetanilide in the later part of the experiments, even though there is an initial stimulation.

Table VIII showing the effects of .I5 percent acetanilid con the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate stated as percents of the normals after a given number of minutes. Time,	Amp.	Rate.	-- Time,	Amp.	Rate.	Notes.
35	I	6.75	.I5	I	III	58	-- 5	III	58	
35	2	6	.I5	"	Io5	Ioo	-- 5	Io6	52	
35	3	8.2	.I5	"	Ioo	Ioo	-- 6	85	87	
35b	I	4.5	.I5	"	Ioo	I2o	-- 4	II5	6I	
35b	2	7	.I5	"	99	Io2	-- 6	8o	85	Strip stopped contracting for one minute just after the drug was removed. Recovery two minutes later.
35b	3	I3	.I5	"	Io3	92	-- 8	49	92	Tone increased to Io7 percent.
36b	I	3.25	.I5	"	Io4	I3o	-- 3	Io3	I3o	
36b	2	I7	.I5	"	Io6	Io2	-- 3	Io2	Io2	Great irregularities occured during the seventh minute.
36b	3	8.5	.I5	"	IIo	75	-- 8	74	4I	Irregularities in both amplitude and rate occured.
36b	4	I3	.I5	"	I24	Ioo	-- 8	I2o	76	
38	I	Io	.I5	"	Io9	Io8	-- 2	II4	I25	
				Same - - - - -			Io	I23	75	
38	2	I2	.I5	"	III	II2	-- 2.5	II6	75	
				Same - - - - -			6	94	75	

Table VIII, continued, showing the effects of .I5 percent acetanilide on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins	Per cent drug	Amplitude and rate stated as percents of the normals of exp. after a given number of minutes. Time	Amp.	Rate	Time	Amp.	Rate	Notes.
36	I	6.5	.I5	I	Io6	I33	4	Io7	I22	
36	2	6.75	.I5	"	IIo	92	5	94	92	
36	3	6	.I5	"	Io4	Ioo	5	III	I2I	
36	4	8	.I5	"	II9	Io8	6	II3	55	
37b	I	Io.5	.I5	"	Ioo	II2	5	Ioo	I25	Very slight irregularities in both amplitude and rate.
37b	2	2I	.I5	"	Io6	Ioo	I8	73	Ioo	
37b	3	I4.5	.I5	"	Io5	Io4	I2	89	Ioo	Slight irregularities occur.
37b	4	23.5	.I5	"	III	Ioo	I.5	II6	Ioo	
37	I	5.5	.I5	"	Io4	Ioo	5	Io2	Ioo	
37	2	I6.5	.I5	"	Io4	Ioo	4	Ioo	Ioo	

The following experiments, (see tables 9& Io), show the result of the application of .2 and .25 percent solutions of acetanilide to contracting heart strips. They are interesting in that these concentrations of the drug stop the contractions of some of the strips to which they are applied. As is seen there is always an increase in amplitude of the contraction, accompanied by a more or less compensating decrease in rate in 5o percent of the experiments in which these percents of the drug is applied. Increase depression as the experiment proceeds holds true in most cases. In two trials, exp. 43, trialI, exp. 44, trialI, table 9, contractions cease while the strip is in the drug solution. The recovery takes place at varying times after the removal of the drug.

An unusual thing occurs in exp. 44, trials 3&4, table 9,. Every second or third contraction is only a few millimeters high, while the normal contractions that preceed and follow theses small ones are many times greater in amplitude. Inco-ordination of the muscle fibers in a contracting heart strip always produces irregularities in the amplitude of the contractions. However if the irregularities in amplitude are great, as they are in the experiment cited above, there is usually an accompanying irregularity in rate, which does not occur in this experiment.

Table IX showing the effects of.2 percent acetanilide on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of the normals.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate stated as percents of the normals after a given number of minutes. Time.	Amp.	Rate.	— Time,	Amp.	Rate	Notes.
43	I	3	.2	I.5	I26	Ioo	2	o	o	Contractions stopped after I.75 minutes.
43	2	6.75	.2	"	II8	Ioo	3	II8	II2	
44	I	6	.2	"	II9	I33	4	I22	66	Contractions ceased after 4.2 minutes. Recovery 6 minutes after the drug is removed.
44	2	5	.2	"	I28	III	4	II7	85	
44	3	7	.2	"	I36	89	6	84	7I	Every other contraction I millimeter in amplitude.
44	4	Io	.2	"	I33	Ioo	8	Io	66	During the last 8 minutes of the experiment there are only three normal contractions. The others were from I to 5 millimeters high.

Table X showing the effects of .25 percent acetanilide on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp' No.	Trial No.	Duration of exp. in mins.	per-cent of drug	Amplitude and rate stated as percents of the normals after a given number of minutes. Time,	Amp.	Rate	-- Time	Amp.	Rate.	Notes.
24	I	2	.25	I	Io4	87	-- I.5	Io6	87	
24	2	I.75	.25	"	Io9	55	-- I.5	II4	5o	
24	3	3	.25	"	Io7	74	-- I.5	II4	66	
24	4	4	.25	"	Io9	85	-- I.5	Ioo	93	
24	5	2.3	.25	"	Io6	4o	--	--	--	Record lost.
24	6	4.2	.25	"	I2o	Ioo	I.5	I2o	62	The slowing and slight irregularity that occured during the experiment stopped as soon as the drug was removed.
4I	I	4.I	.25	"	II8	73	3	II8	66	
4I	2	4.6	.25	"	Io9	Ioo	3	Io2	9o	

The results obtained when .3 and .35 percents of acetanilide are used are marked because in most cases,(in 93 percent of the cases) , there is cessation of the contractions of the heart strips to which they are applied . This quiesence is preceeded usually by signs of depression shown upon the rhythm. The time of the recovery of the lost automatic contractions is roughly proportional to the length of time the strips are exposed to the acetanilide solution. In no case is there failure of recovery. That which seems to be evidence of stimulation as shown by the amplitude of the contractions of the strips in tables II and I2, is beyond doubt largely compensatory for the decrease in rate. An interesting result , differing from all the others, is seen in exp. 46b, trial2, table II, in which the depressant effect appears to fall on the amplitude and the compensating increase shows in the rate which is maintained so that the pause which occurs in every other case with this strength of the drug,(.3 percent) does not follow in this case.

Table XII showing the effects of .3 percent acetanilide on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Per cent of drug.	Amplitude and rate stated as percents of the normals, after a given number of minutes. Time,	Amp.	Rate.	-- Time,	Amp.	Rate.	Notes.
45b	I	I5.7	.3	I.5	II8	Ioo	--	Io	Io2	5o	Contractions ceased after I3 minutes. Recovery Io minutes after removal of the drug.
45b	2	8	.3	"	I22	72	--	6	8o	78	Contractions ceased after 7 minuts following long periods of relaxation. Recovery upon the remov- of the drug.
46b	I	36	.3	"	IIo	25	--	4	II3	66	There were great irregularities in rhythm Contractions ceased after 3I minutes. Recovery in 5 minutes.
46b	2	35	.3	"	83	Io5	--	4	56	I5o	Typical NaCl tracing.
47b	I	24	.3	"	IIo	Ioo	--	5	I2I	62	Contractions ceased after I9 minutes. Recovery in 5 minutes.
47b	2	39	.3	"	III	42	--	2.5	o	o	Contractions stopped after 2.33 minutes. Recovery in I2 minutes.
49b	I	86	.3	"	II3	93	--	4	I3o	52	Contractions stopped at the end of I8 and 3o minutes. Recovery in 26 minutes.
49b	2	2o.5	.3	"	o	o	--	5	Io2	Ioo	Contractions first stopped at the end ofI minute. Upon being stimulated they began, they stopped in I9 minutes. Recovery in 2.5.

Table XII showing the effects of .35 percent acetanilide on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp' No.	Trial, No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate stated as percents of the normals, after a given number of minutes. Time, Amp. Rate			— Time, Amp, Rate.			Notes.
50b	I	I4	.35	I.5	I25	57	— 5	I36	68	Contractions ceased after 8 minutes. Recovery in 22 monutes.
50b	2	6	.35	"	III	64	— 3	IoI	92	Contractions first stopped after .5minutes for I minute. They began again without external stimulation, and stopped at the end of 3 minutes. Recovery in 3 minutes.
50b	3	I4.5	.35	"	Io3	Ioo	— 3.2	96	5o	Contractions stopped at the end of 3.5 minutes. Recovery in 6 minutes.
50b	4	8.5	.35	"	I4o	Ioo	— 5	I64	4o	Contractions ceased in 3.5 minutes.
5Ib	I	4.75	.35	"	I3o	IIo	(last 3 mins. —	I55	66	Contractions ceased after 4.25 minutes. Recovery in 3 minutes.
52b	I	6.75	.35	"	II6	58	— 4	Io6	Ioo	Contractions ceased at 9 minutes. Recovery in 22 minutes
52b	2	8	.35	"	II5	8o	— 3	Io9	9o	Contractions ceased at 3.5 minutes. Recovery in 9 minutes.

Acetanilide in .4 percent solution in addition to stopping the visible activity of the comtracting strip to which it is applied, as did the lower percentages, .3 and .35 percents, it causes an increase in tone varying from 102 to 116 percents, (see tables 13). The initial stimulation which is usually evident, is succeeded shortly by signs of depression before complete cessation of activity occurs.

With this strong solution of acetanilide, which is evidently toxic there are no results suggesting that the drug is cumulative in its effects. Rather one might easily conclude that the strips repeatedly exposed to the drug develop a tolerance. The length of time which the strips, bathed in .4 percent acetanilide continue their automatic contractions before the rhythm ceases is greater the last half of the series than the first, (see table 13). The time of the recovery in the first two trials, though not stated in minutes, must have no less than fifteen minutes and no greater than thirty minutes. The recovery time in the latter part of the experiment is from one to two minutes. Hale(9) found, in experimental work on the action of acetanilide on the frog's heart, that a " peculiar feature of acetanilide poisoning is that the effect of the drug appears to grow less in certain instances, so that the rate and sometimes the output were secondarily augmented, although never was a normal or even nearly normal action regained.

One may conclude that the strips subjected to .4 percent acetanilide are not permanently poisoned, for recovery is the rule. There is evidence that the heart tissue attains a certain degree of tolerance for the drug.

Table XIII showing the effects of .4 percent acetanilide on the amp- and rate of one strip of terrapin9s ventricle contracting in Ringer s solution. The results are figured as percents of normal.

Exp. No/	Trial No.	Duration of exp. in mins.	Per- cent of drug.	Amplitude and rate stated as percents of the normals, after a given number of minutes. Time, Amp. Rate -- Time, Amp. Rate.							Notes.
25	I	2.5	.4	I	Ioo	I33	--	I.5	Io2	III	Contractions stopped after I.6 minutes. General Tone Io8 percent. Recovery after Ringer and NaCl bath.
25	2	I.6	.4	"	IoI	I2o	--	I.5	o	o	Contractions stopped after I.2 minutes General tone Io6 percent. Recovery aafter Ringer and NaCl bath.
25	3	I	.4	"	o	o	--	I.5	o	o	Contractions stopped after .8 minutes. General tone II6 percent. Recovery after .8 minute.
25	4	2.9	.4	"	93	I36	--	I.5	87	I5o	Contractions stopped after I.7 minute General tone IIo.
25	5	5.7	.4	"	Ioo	Ioo	--	I.5	97	85	Contractions stopped after 5 minutes. General tone Io3 percent. Recovery in I. I.7 minutes.
25	7	4	.4	"	Io6	8I	--	I.5	96	57	Contractions stopped after 3.7 minute General tone Io2 percent. Recovery in 2 minutes.
25	9	5.5	.4	"	I36	Ioo	--	I.5	I22	88	Contractions stopped after 4 minutes. General tone II5 percent.

Acetanilide is only soluble to the extent of one part in two hundred parts of water. Although weaker solutions than .5 percent are evidently toxic, this higher percent may well be used for the purpose of accentuating the results obtained upon the application of the weaker toxic solutions of the drug to contracting strips. The most marked result over those obtained by the use of the weaker solutions, is the great increase in general tone shown by the ventricular strips upon being subjected to a .5 percent solution of acetanilide. The average increase in six different strips is 175 percent of the normal tone. The same general picture shows on the record in all the trials of this strength of the drug. There is evident depression in general efficiency from the first, and usally this increases as the bath proceeds. There is a continuous rise in the base line accompanied by a decrease in the amplitude of the contractions. The cessation of the contractions comes, usually when the tone is at its greatest. During the pause there may or may not be a more or less dropping in the tone, the rhythm, however is rarely resumed until the normal or a subnormal degree of tone is reached. When rhythm is resumed, the amplitude of the contractions seems quite normal, as does often, the rhythm. Trial after trial can be made of the action of the drug on a ventridular strip, quiesence will follow from which recovery can be gotten upon the removal of the drug, yet no cumulative action will be visible. In exp. 43b, trials 2, 3 and 4 are followed only by a great slowing in one case and by slight slowing in the others although the preceeding application of the drug brought about temporary cessation of activity of the strip. Only in one case is there failure of recovery, (exp.43b, trial2, table I4). On this occasion shortly after the removal of the drug solution this strip was left suspended in the air instead of in the normal Ringer's solution, by which the

drug might have been washed out and it was also stimulated by electricity. this proceedure may have been responsible for the failure to recover automatic contractions. The responses given to electrical stimulation were quite normal in amplitude.

One may conclude that this drug, acetanilide, gives no evidence of being cumulative in its action. The heart tissue either develops a tolerance of it or the mode of union of the drug with the tissue is not one that leaves permanent injury.

Table XIV Showing the effects of .5 percent acetanilide on the amplitude and the rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate stated as percents of the normals, after a given number of minutes. Time,	Amp.	Rate,	Time	Amp.	Rate.	Notes.
39b	I	7	.5	I.5	II3	8o.5	5.25	8o.3	Io9	Contractions stopped after 5.25 minutes. Generalttone II2 per cent. Recovery in I2 minutes.
4ob	I	I2	.5	"	98	Io7	II	7o.3	2o	Contractions stopped after II minutes General tone 32o per cent. Recovery in 3 minutes.
4ob	2	2I	.5	"	Ioo	I57	Io	56	84	Contractions stopped after Io minutes General tone I9o per cent. Recovery in 2I minutes.
42b	I	I5.5	.5	"	Io8	52	3	Io6	7	Contractions stopped after 4 minutes General tone I6o per cent. Recovery in I minute.
42b	2	4.75	.5	"	88	Ioo	3.5	76	4I	Contractions stopped after 3.5 minutes. General tone I92 percent. Recovery in 6.5 minutes.
42b	3	5	.5	"	96	59	4	8o	lost	Contractions stopped after 4 minutes. General tone I57 per cent. Recovery in II minutes.
42b	4	8	.5	"	o	o	4	87	45	Contractions stopped after I minute. They recovered after I.5 minutes, and stopped again at the end of 6 minutes. General tone I55 per cent.

Table XIV, continued, showing the effects of .5 percent acetanilide on the amplitude and the rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate stated as percents as percents of the normals after a given number of minutes. Time	Amp.	Rate	-- Time,	Amp.	Rate.	Notes.
41b	I	19	.5	1.5	74	83	-- 7	21	62	Contractions stopped after 18 minutes General tone 306 percent. Recovery in 21 minutes.
43b	I	3	.5	"	138	60	-- 2.6	0	0	Contractions stopped after 2.5 minutes General tone 110 percent. Recovery 2.5 minutes.
43b	2	5.5	.5	"	116	28	-- 2.25	70	15	Contractions stopped after 2.5 minutes. General tone 133 percent. Recovery never.
44b	I	6	.5	"	125	88	-- 3	88	127	Contractions stopped after 3.5 minutes General tone 91 percent. Recovery in 21 minutes.
24b	I	2	.5	"	122	83	-- 1.5	128	83	Contractions stopped after 2 minutes. Recovery in 1.5 minutes.
24b	2	1.7	.5	"	103	138	-- 1.5	101	111	There was great slowing 1 minute after the drug was removed.
24b	3	3	.5	"	106	117	-- 1.5	0	0	Contractions stop- after 2 minutes. Recovery after 30 minute
24b	4	1.8	.5	"	108	86	-- 1.5	109	100	Slight slowing followed the removal of the drug.

Chart I showing the averaged effects of a series of applications of each of the following percents of acetanilide, .01, .02, .03, .04, .05, to a contracting strip of terrapin's ventricle.

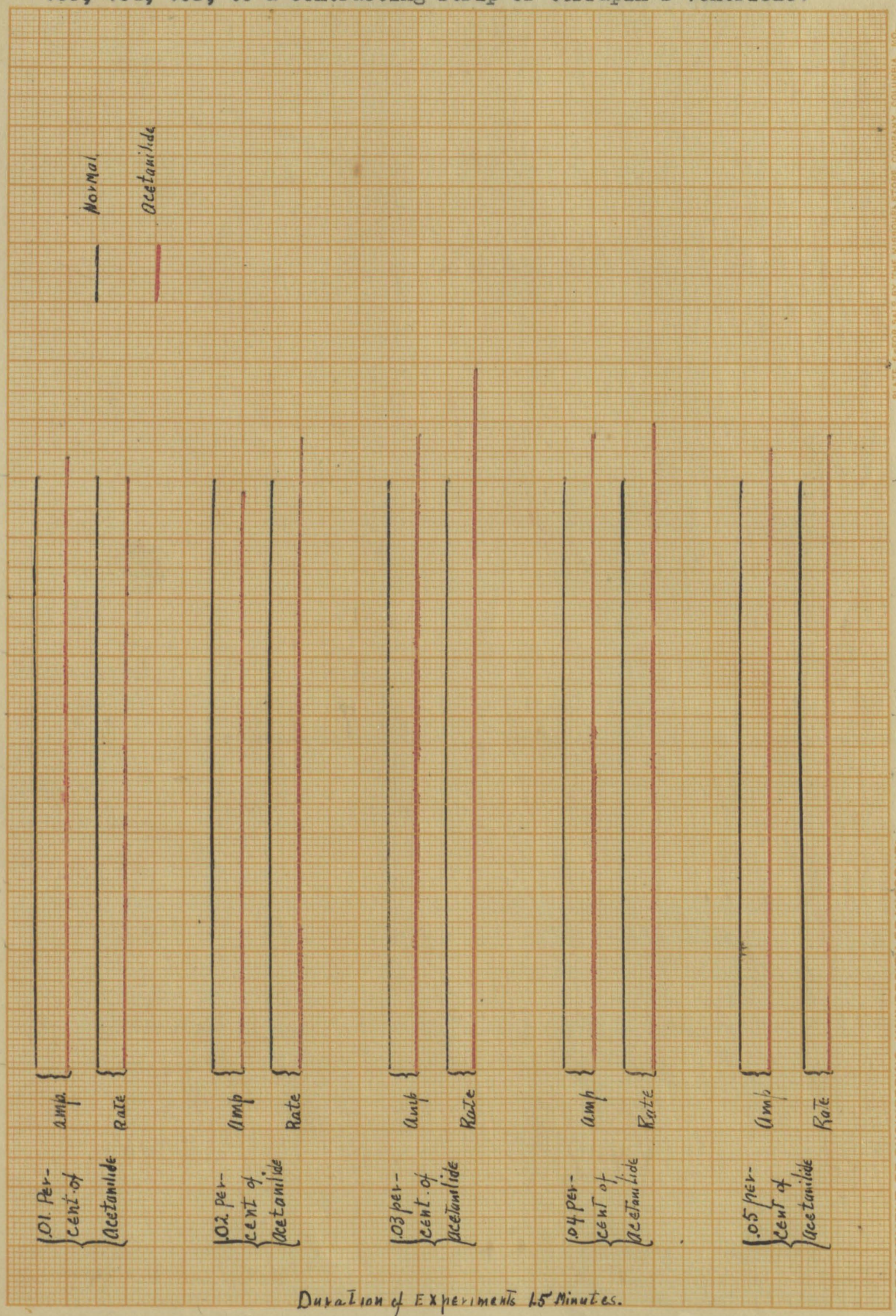

Chart I

Chart II showing the averaged effects of a series of applications of each of the following percents of acetanilide, .I, .I2, .I5, .2, .25, to a contracting strip of terrapin's ventricle.

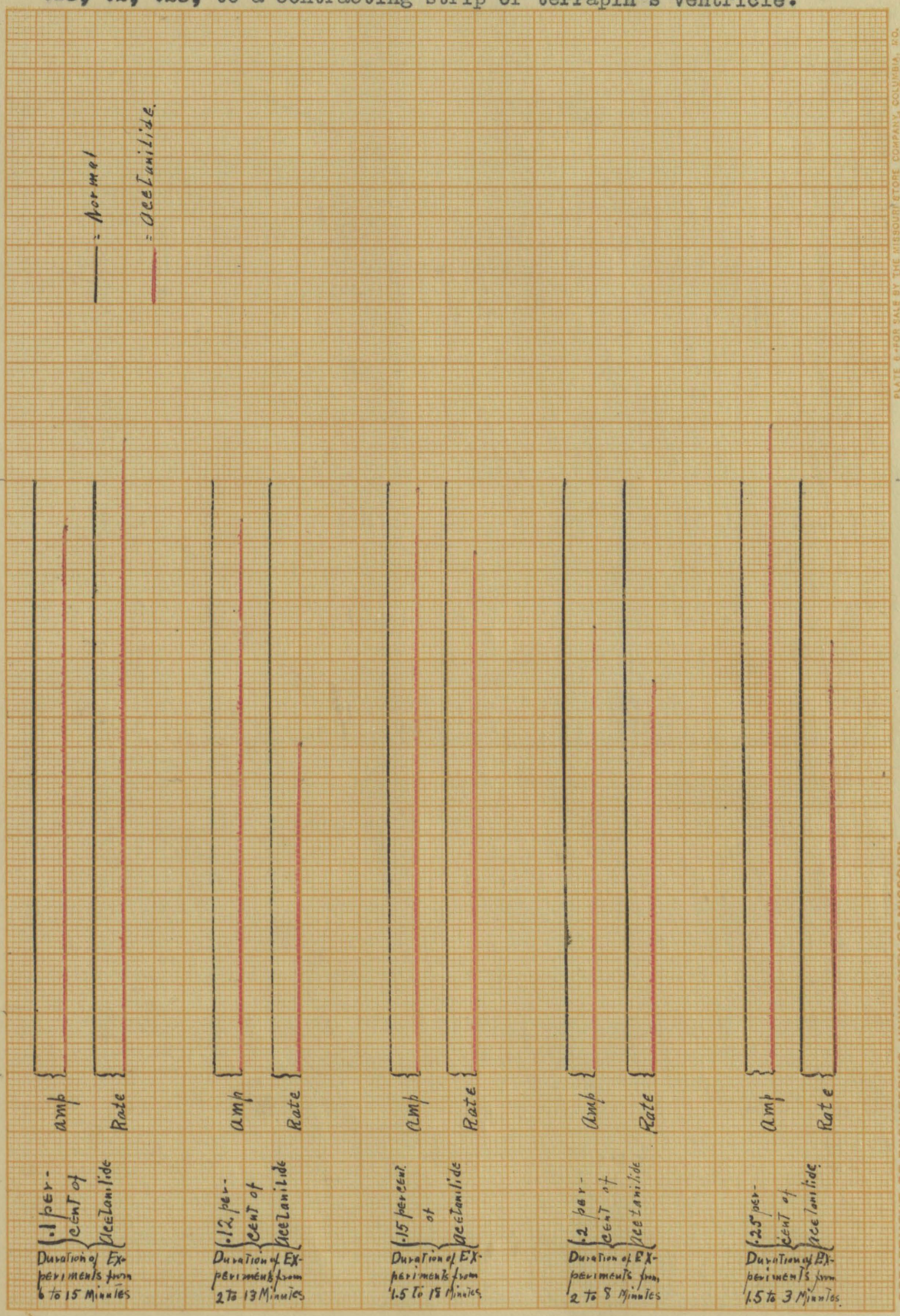

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Chart II

Chart III showing the averaged effects of a series of applications of each of the following percents of acetanilide, .3, .35, .4, .5, to a contracting strip of terrapin's ventricle.

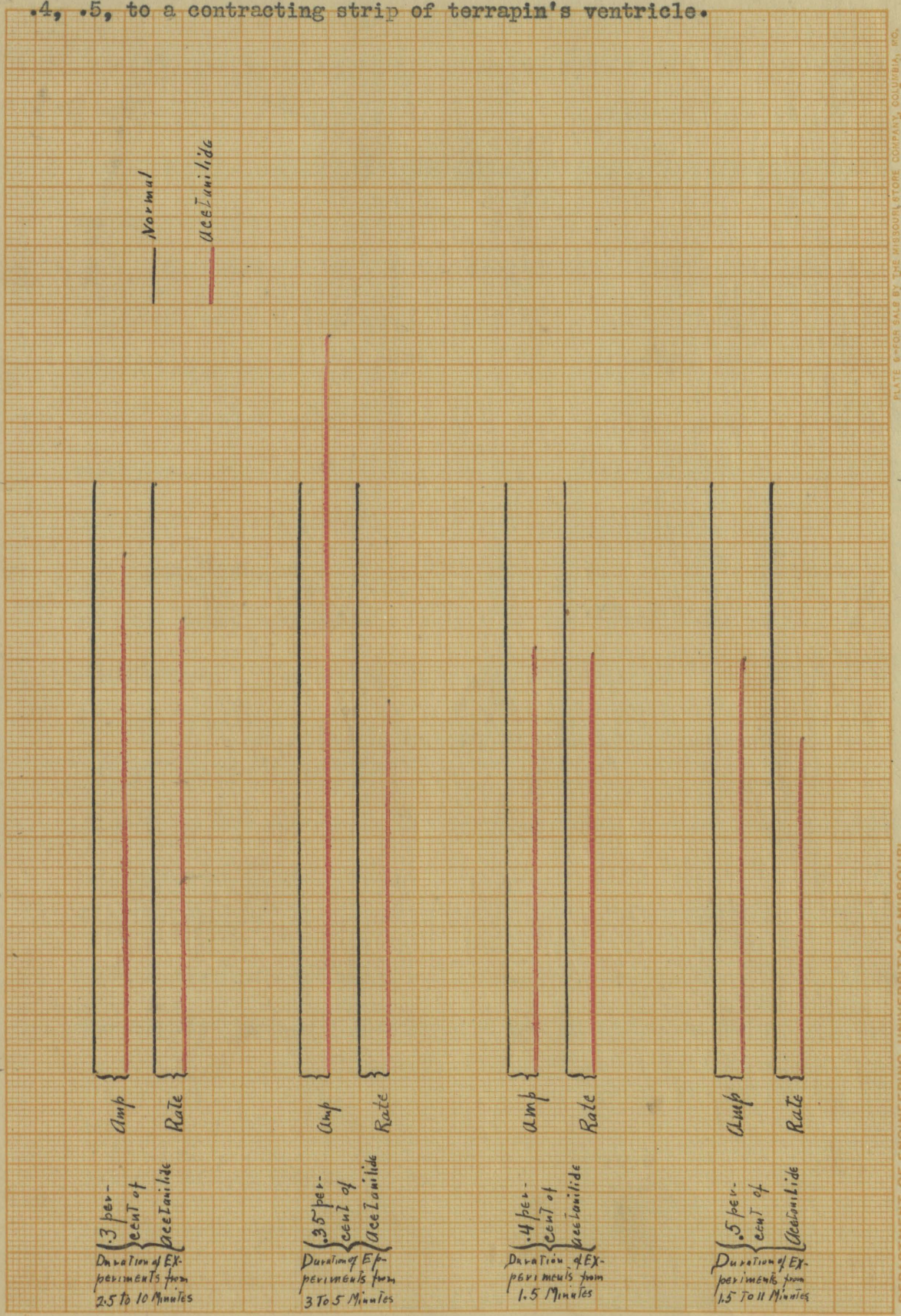

Chart III

Summary of the Action of Acetanilide on Ventricular Muscle.

I, The action of acetanilide on ventricular muscle varies according to the concentration in which it is applied.

2, Strengths of .o3 and .o5 percents, (tables 3, 4 and 5), cause a maximal but relatively small amount of stimulation shown in both the amplitude and rate.

3, Weaker strengths, .oI to .o2 percents, (tables I and 2), in most cases results only in a minimal amount of stimulation of either amplitude or rate or both.

4, Stronger solutions of acetanilide, .I to .5 percents,(tables 6 to I4), cause depression of the rate and amplitude following an initial stimulation. The stimulative stage varies greatly in amount and is often absent. The depression, (tables 9 to I4), amounts to a complete suppression of the rhythm in most trials of solutions of .3 percent and stronger.

5, The fact that .I and .I2 percents of acetanilide,(tables 6 and 7) stimulate and later depress the strip suggests that the drug cumulative, however since a series of exposures of one strip to acetanilide do not show a cumulated effect, it is improbable that it would be evident during one application. The depressing effect following the initial stimulation may be consistently explained by supposing that in the first part of the bath just enough of the drug has diffused into the strip to cause stimulation and as the bath proceeds the drug continues to combine in greater amounts with the tissue and causes depression. This idea is upheld also by the

fact, an isolated case in table 2, when .o2 percent of acetanilide is applied to the heart strip, minimal occurs but upon continuing the experiment long enough maximal stimulation results.

6, No evident , irreparable injury is wrought upon the muscle in most instances by the more toxic strengths of acetanilide, provided that the application is short and the drug solution is removed immediately or shortly after the rhythm ceases. The longer the union of acetanilide with the ventricular strip, beyond certain limits, the less certain is the recovery of the tissues in the normal solution.

7, The evidence of the development of tolerance of acetanilide by the ventricular strip does not seem to be conclusive, In a great many cases, however, a semblance of tolerance is present.

8, The fact that rhythmic contractions are not resumed, following a pause in acetanilide ,until there is a dropping of the increased tone to a normal or a subnormal amount supports Lingle's theory of tone.

Action of acetanilide on Contracting Sinus Strips.

Comparative data of the actions of varying percents of acetanilide on contracting sinus strips are hard to collect. To be able to make any relative estimates of its influence it seems necessary to consider the amp- and the rate of the tone waves and the general tone of the strip during the whole time of a single application of the drug, rather than at certain intervals during the experiment, as was done in the case of the experiments on the ventricular muscle.

The weaker solutions of acetanilide .oI to .o5 percents, (tables I to 5), all affect the contracting sinus strip markedly. The rhythm and tone are depressed; only one isolated exception to this rule is seen , in exp. 5o, trial 2 table 3) and this is followed by great and permanent depression in the general tone after the acetanilide is removed. The recovery from this usual depression is seldom complete. In three cases, restoration to the former condition is attained as is seen in exp.38, trial I, table I; exp.5I, trial 2, table 4; exp. 46, trial I, table 5. There is no evidence of a cumulative effect of acetanilide when used in successive experiments in these weaker percentages, .oI to .o5.

There is an evident tendency to an increase in amplitude of the tone waves going hand in hand with a decrease in general tone and vice versa. Exp. 49 , trials I, 2 and 3, table 2 indicate this. This fact is in line with Lingle's theory of tone. According to this theory the greater the number of elements involved in producing an increase in general tone

the fewer there will be for mediating tone rhythms. It is interesting to note, too, that in exp. 5I, trials I & 2, table 4, where fundamental contractions are visible that they become greater in amplitude as the general tone decreases. In normal tissues whenever primary contractions are shown along with rhythmic tone contractions, they decrease in amplitude as the tone waves increase in amplitude and vice versa. This still remains true when the tissue is under the influence of acetanilide.

Tables I and II showing the effectsof .oI and .o2 percents of acetanilide on the amplitude and rate of tone waves of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial NO.	Duration of exp. in mins.	Percent of drug	Amplitude and rate of tone waves during the experiment stated as percents of the normals. Amp.	Rate.	General tone stated in percent of normal.	Notes.
48	I	36	.oI	43	7o	7o	The tone waves seemed to recover fully after the experiment. General tone fully recovered.
47	I	35	.oI	88	33	85	The tone waves grew slower as the experiment proceeded. Recovery of tone waves fairly good General tone 79 percent of normal.
Table II							
49	I	2o	.o2	I2I	78	8o	The tone waves fully recovered. General tone never recovered fully.
49	2	II	.o2	I37	I8	7	As the general tone fell the individual waves grew larger. There was never a complete recovery in general tone or tone waves.
49	3	Io.5	.o2	Io4	2	4	After the first 4 minutes, the tone waves die out and never recover the original rhythm. The general tone recovered.

* Note; An average of the greatest and the least degrees of tone in the normal and the average in the drugged strip was taken for the general tone

Tables III and IV showing the effects of .o3 and .o4 percents of acetanilide on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Per cent of drug	Amplitude and rate of tone waves during the experiment stated as percents of the normals. Amp.	Rate.	General tone stated in percent of normal.	Notes.
5o	I	Io.5	.o3	67	89	94	Tone waves recovered though greater in amplitude and less in rhythm. General tone recovered.
5o	2	8	.o3	79	I3I	I3o	Five minutes after the bath the tone fell permanently to 47 percent. Slow and deep tone waves followed.
Table IV							
5I	I	8.5	.o4	64	46	89	Tone waves did not make over 5o percent recovery. Fundamental contractions which had been barely visible, became greater in amplitude as the general tone decreased. General tone recovered.
5I	2	8.5	.o4	64	Ioo	IoI	Recovery of tone waves and general tone I4 minutes after the drug bath.
5I	3	I8.5	.o4	83	35	29	Tone waves recovered immediately after the drug was removed.

Table V showing the effects of .05 percent of acetanilide on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate of tone waves during the experiment stated as percents of the normals. Amp.	Rate.	General tone stated in percent of normal	Notes.
45	I	Io	.05	2I	IIo	62	Recovery of tone waves in the 3rd minute after the bath. Recovery of general tone 67 percent.
46	I	26	.05	7I	7I	II4	Former rate of tone waves never recovered till after I hour of Ringer bath.
46	2	25	.05	58	42	73	Recovery of tone waves I4 minutes after the experiment. general tone 84 percent.
46	3	I4	.05	22	Io7	55	Recovery I8 minutes after the experiment.

As the strength of acetanilide is increased, the depression resulting upon its application to a contracting sinus strip is more regular and is more consistent. However it falls more upon the rhythm than on the amplitude. The general tone is never recovered completely, as is possible when the weaker solutions,discussed above , are used.

There is comparatively little difference shown in the degree of depression of the sinus strip during the application of .I percent acetanilide and that of the weaker percentages, .oI to .o5 percents. But the recovery of the tissue from the exposure to the .I percent solution is much slower and less complete than that following the subjection of the strip to .oI to .o5 percents. The deferred recovery and failure of recovery of the rhythmic tone waves after the use of .I percent acetanilide,(see exp.34,trial2; exp.46, trial2, table 6), suggests again that acetanilide is cumulative in its action It is impossible to decide whether this is the case in these instances or whether, as in the example of the ventricular strip,(see pages I6 and I7), the injury wrought by the first exposure to acetanilide has lowered the resistance and therefore increased the relative toxicity of that percent of the drug.

This cumulative effect of acetanilide, or the semblance of it is produced also by .I2 and .I5 percent solutions. After a succession of trials there is either complete cessation of tone waves, with no recovery or only partial recovery, or great depression followed by uncertain and slow recovery. Equal depression of the general tone does not accompany the fall in the number of the tone contractions.

Table VI showing the effects of .I percent of acetanilide on the amplitude and the rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate of tone waves during the experiment stated as percents of the normal. Amp.	Rate	General tone stated in percent of normal	Notes.
34	I	Io.5	.I	76	42	I8	Recovery of general tone was not more than 5o percent at any time. The tone waves continued with a slower rhythm.
34	2	8.5	.I	Io5	33	I8	Tone waves did not recover until after 2 hours in Ringer. General tone 4o percent of normal.
4o	I	9.4	.I	4o	62	64	Slight tone waves were recovered 8 minutes after the experiment. General tone was 25 percent of normal.
4o	2	II.5	.I	8o	I6	8o	Tone waves died out completely. General tone tone 58 percent of normal.
42	I	Io	.I	I62	58	72	No loss in tone waves during the experiment. General Tone 63 percent of normal.
42	2	I6	.I	59	54	77	Fairly good recovery 7 minutes later. General tone 22 percent of normal.

Table VII showing the effects of .I2 percent of acetanilide on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Per cent of drug	Amplitude and rate of tone waves during the experiment stated as perments of the normal. Amp.	Rate.	General tone stated in percent of normal.	Notes.
3o	I	6	.I2	Io	25	I8	Recovery of tone waves 9 minutes after the experiment. General tone 77 percent of normal.
3o	2	3.2	.I2	6.3	33	45	Recovery of tone waves 4.5 minutes after the experiment. General tone 73 percent of normal.
3o	3	4.75		79	34	86	Recovery of tone waves 2 minutes after the experiment. General tone II2 percent of normal.
3o	4	7		I43	2I	28	Recovery of tone waves 9 minutes after the experiment. General tone 46 percent of normal.
3o	5	9.5		o	o	22	Recovery of tone waves I2 minutes after the experiment.
32	I	Io.5		I47	56	28	Recovery of tone waves I5 minutes after the experiment.
32	2	6		Io3	25.5	8I	Recovery of tone waves II minutes after the experiment.

Table VII continued, showing the effects of .I2 percent of acetanilide on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution . The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate of tone wanes during the experiment stated as percents of the normal. Amp.	Rate	General tone stated in percents of	Notes.
32	3	5	.I2	o	o	52	Recovery of tone waves I2 minutes after the experiment. General tone 55 percent of normal.
32	4	5	.I2	o	o	I8	No recovery of tone waves or general tone in I8 minutes after the experiment.
33	I	5.5	.I2	I37	5o	55	Recovery of tone waves 2 minutes after the experiment. General 27 percent of normal.
33	2	7	.I2	97	7I	55	Recovery of tone waves 3 minutes after the experiment. General tone 28 percent of normal.
33	3	I2.5	.I2	88	33	2.5	No signs of recovery Io minutes after the experiment.

Table VIII showing the effects of I5 percent of acetanilide on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate of tone waves during the experiment stated as percents of the normal. Amp.	Rate.	General tone stated in percents of normal.	Notes.
35	I	6.75	.I5	88	55	63	Recovery of tone waves immediately. General tone data lost.
35	2	6	.I5	o	o	6I	Recovery of tone waves 5 minutes after removal of the drug. General 42 percent of normal.
35	3	8.2	.I5	6o	5o	33	No recovery within 3o minutes.
36	I	3.25	.I5	6	I6	6	Recovery after 9 minutes. General tone 53 percent of normal.
36	2	I7	.I5	LI2	29	47	Recovery of tone waves Io minutes after the removal of the drug. General tone 8 percent of normal.
36	3	8.5	.I5	o	o	65	Recovery of tone waves I3 minutes after removal of the drug. General tone 72 percent of normal.
36	4	I3	.I5	o	o	62	Recovery of tone waves L5 minutes after the experiment. General tone 67 percent of normal.
38	I	Io	.I5	o	o	65	Recovery of tone waves I5 minutes after the experiment. General tone 28 percent of normal.

The experiments showing the reactions of the sinus strip to .2 and .25 percent of acetanilide solutions are hard to interpret(tables9 and Io). A general tendency toward an accumulative action of the drug is indicated by the lessened degree and the lengthened time of the recovery, and also by the greater depression of the activity of the sinus toward the end of a series of tests on the same preparation. The influence of these strengths appears to be no greater than that of .I2 to .I5 percent solutions. Even the stronger and more toxic solutions of .4 and .5 percents scarcely any greater effects during the application of the drug . The degree and the rapidity of recovery however, are much affected. No recovery is made except after repeated washings with normal solutions,-with physiological saline and with Ringer. Often no recovery occurs either of the tone or fundamental rhythm.

Table IX showing the effects of .2 percent of acetanilide on the amplitude and rate of a terrapin's sinus contracting in Ringer' s solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug.	Amplitude and rate of tone waves during the experiment stated as percents of the normal. Amp.	Rate.	General tone stated in percents of normal.	Notes.
43	I	3	.2	I4	38.6	8o	Recovery of tone waves 6 minutes after the experiment. General tone 65 percent of normal.
43	2	6.75	.2	88	I9	7o	Recovery of tone waves 9 minutes after the experiment. General tone 22 percent of normal.
44	I	6	.2	II5	66	54	Recovery of tone waves 2 minutes after the experiment. General tone Io percent.
44	2	5	.2	I4	4o	29	Recovery of tone waves I9 minutes after the experiment. General tone 4I percent.
44	3	7	.2	o	o	8o	Recovery of tone waves I6 minutes after the experiment. General tone 48 percent of normal.
44	4	Io	.2	I7I	2o	67	No recovery 9 minutes after the experiment.

Table X showing the effects of .25 percent of acetanilide on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug.	Amplitude and rate of tone waves during the experiment stated as percents of the normal. Amp.	Rate.	General tone stated in percents of normal.	Notes.
4I	I	4.I	.25	I7	Ioo	26	Recovery of tone waves I8 minutes after the experiment.
4I	2	4.6	.25	o	o	I	Tone waves were recovered 22 minutes after the experiment.
24	I	2	.25	I4I	Ioo	62	Lost record.
24	2	I.75	.25	Ioo	I25	Ioo	Recovery of tone waves 2 minutes after the experiment. General tone 4o percent of normal. Primary contractions were shown Amp. I25 percent of normal, rate Ioo percent of normal.
24	3	3	.25	Ioo	33	IIo	Recovery of tone waves 2 minutes after the experiment. General tone 23 percent of normal. Primary contractions were seen .
24	4	4	.25	75	3o	8I	Recovery of tone waves 5 minutes after the experiment. General tone 53 percent of normal.
24	6	4.2	.25	IoI	23	4I	Recovery of tone waves 3 minutes after the experiment. General tone 9o percent of normal.

Tables XI andX XII showing the effects of .4 and .5 percents of acetanilide on the amplitude and the rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Table XI,

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate of tone waves during the experiment stated as percents of the normal. Amp.	Rate	General tone stated in percents of normal.	Notes.
25	I	2.5	.4	I4	5o	Io9	Recovery of tone waves only after a NaCl and a Ringer bath. General tone 27 percent of normal, 4 minutes after the removal of of the drug.
25	2	I.6	.4	67	I25	74	Recovery of tone waves only after a NaCl and a Ringer bath. General tone 8 percent of normal 3 minutes after removal of the drug.
25	3	I	.4	43	I3o	78	No recovery.

Table XII

24	I	2	.5	9o	83	8I	No recovery during the following 6 trials. Slight recovery later.

Summary of the Action of Acetanilide on Contracting Sinus Strips.

I, The weakest solutions of acetanilide used, .oI to.o5 percents, markedly affect the activities of the sinus, usually by depressing the amplitude and the rate of the tone waves, and also diminishing the general tone.

2, There is evidence of cumulative action of acetanilide which may be due to lowered vitality of the strip.

3, As the strength of the acetanilide, which is applied to the strip, is increased, the effect is shown on the time of the period and the degree of the recovery of the strip after the application of the drug rather than upon the responding activities of the strip during the exposure to the acetanilide.

Experiments to Test the Degree of Irritability of the Ventricular Strip During Acetanilide Pause.

In order to get some evidence of the condition of the ventricular strip when its automaticity has ceased during the subjection to toxic solutions of acetanilide and during the subsequent recovery in the normal solution, the irritability and efficiency of the muscle for contraction were tested at short intervals by electric currents sent through the strip. The tissue to be tested was mounted in the usual way, with the exception t that fine copper wire insulated with paraffin was used for suspension in place of the usual threads. This enabled one to stimulate the strip without removing it from the surrounding solution or distirbing it in any way.

After there was cessation of contractions in the drug solution a series of single break stimuli were sent through the strip at varying intervals of time. The strength of the stimuli began with the secondary of the inductorium (Harvard type), at Io centimeters, and was gradually increased until a response was given by the muscle. The strength of the stimulus causing a contraction in each case was called the minimal stimulus. When the drug solution was removed the condition of the strip was tested in the same manner as it recovered in the normal solution.

If the cessation of contractions be due to decreased irritability and the power of conduction of the strip rather than to the injury of the contractile elements, one should get evidence of it from this experiment. Moreover, it is to be expected that as the bath of acetanilide is prolonged the irritability of the strip will be more and more decreased, and vice versa when the drug solution has been replaced and is being washed out by the normal

solution. This latter expectation proves true in exp. 50b , trials 2, 3 and 4. In trial I a slight deviation from this rule is seen though the general trend of the reaction is in the same direction. In exp. 49b, trial I, table I, the irritability of the strip as indicated by the strength of the minimal stimulus, is increased at first in the drug solution but later is decreased as the experiment proceeds. The irritability of the strip during the recovery from this exposure is more uniform than during the exposure. The irritability is gradually increased,with few exceptions only, as the acetanilide is being washed out. A greater deviation from this rule, stated at the beginning of the paragraph, may be seen in exp. 52b, table 3, where the irritability is not progressively decreased during the depression caused by the drug nor is it progressively increased during the recovery in the normal solution. Never-the -less the depression is greater at the end of six minutes than at the end of two minutes after the acetanilide pause began. It is true also that the recovery is not marked by regular increases of irritability, though the condition of the strip is better at the end of twelve minutes than it is two minutes after the removal of the drug. There are some three or four of such cases as this one cited above.

Table I showing the relative irritability and efficiency for contraction of the ventricular strip during and after the first application of .3 percent of acetanilide as tested by the minimal stimulus method.

Exp. 49b, Trial I.

Time of stimulation stated in minutes after the acetanilide pause began.	Minimal single break induction effective stated in C.M on the induction coil.	Amplitude of resulting contraction stated as the percent of normal.	Notes.
2			
2	o	86	
4	o	o	
4.75	3	78	
6	6 (6 stimuli per seconds)	9I	
I8	5.5(" "	Ioo	
24	6	97	
28.5	I	Ioo	
32.5	4	Ioo	
47.5	I.5	Ioo	Relaxation much slower.
55	I.5	97	
Time of stimulation stated in minutes after the removal of the drug.			
I.2	o	o	
2.5	2.5	Io4	
3	2.5	Io2	
4	3	Ioo	
4.5	4	Ioo	
6	4.5	Ioo	
8.5	4	Ioo	
9	5	Ioo	
Io.5	3	Io4	
II	4.5	Io2	
I2	5	Io4	
2o	3.5	88	

Cont.-

Table I, continued, showing the relative irritability and efficiency for contraction of the ventricular strip during and after the first application of .3 percent of acetanilide as tested by the minimal stimulus method.

Exp. 49b Trial I continued.

Time of stimulation stated in minutes after the removal of the drug	Minimal single break induction effective stated in C.M. onthe induction coil.	Amplitude of resulting contraction stated as the percent of normal.	Notes.
2o.5	4	88	
22	5.5	88	
25	6	88	
25.5	8	88	Automatic contractions followed this stimulation.

In the initial latent period of this strip stimuli of

o C.M. caused no contraction.

I " " " subnormal contraction.

5 " " " " " .

6.5 " " " " " .

In the quiescence following the first application of the drug

3 C.M. caused a subnormal contraction.

I " " " " " .

Table II showing the relative irritability and efficiency for contraction of the ventricular strip during and after the first application of .35 percent of acetanilide as tested by the minimal stimulus method.

Exp. 5ob, Trial I.

Time of stimulation stated in minutes after the acetanilide pause began.	Minimal single break induction effective stated in C.M. on the induction coil.	Amplitude of resulting contraction stated as the percent of normal.	Notes.
I	3.5	89	
2.5	.5	95	
5	I.5	II2	
Time of stimulation stated in minutes after the removal of the drug.			
7	o	4	
7.2	o	4	This was followed by automatic contractions of Amplitude I75 percent of normal. Rate 46 percent of normal

In the initial latent period of this strip minimal stimuli of

I C.M. caused a contraction of I2 millimeters.
o " " " " " " I2 " .

In the quiesence of the strip caused by the first application of .35 percent acetanilide , minimal stimuli of

3.5 C.M. caused a contraction of 2I millimeters.
I.5 " " " " " 27 " .

Table II continued, showing the relative irritability and efficiency for contraction of the ventricular strip during and after the application of ·35 percent of acetanilide as tested by the minimal stimulus method.

Exp. 5ob trials 2 and 3.

Time of stimulation stated in minutes after the acetanilide pause began	Minimal single break induction effective stated in C.M. on the induction coil.	Amplitude of resulting contraction stated as the percent of normal.	Notes.
.8	3	94	
I.5	o	97	
3	2.5	Io2	
4	4.5	Io7	
Exp. 5o.Trial 3			
I	4.5	79	
2	4.5	79	
3	4.5	79	
5	2.5	84	
6	3	8o	
8	2	84	
9.7	I	84	
Time of stimulation stated in minutes after the removal of the drug.			
2.5	I.5	I29	
3	2	I29	
3.75	2.5	I29	

Table III, showing the relative irritability and efficiency for contraction of the ventricular strip during and afetr the application of .35 percent of acetanilide as tested by the minimal stimulus method.

Exp. 52b.Trial I.

Time of stimulation stated in minutes after the acetanilide pause began	Minimal single break induction effective stated in C.M. on the induction coil	Amplitude of resulting contraction stated as percent of normal.	Notes.
2	3.5	Io6	
3.5	5	Io6	
6	2	I2o	
Time of stimulation stated in minutes after the removal of the drug.			
2.6	3.5	I46	
3.3	2	I46	
5.5	2.5	I46	
8.5	I.5	I46	
Io	4	6	
I2	3.5	I46	Recovery of rhythm 25 minutes after removal from the drug and upon the application of a NaCl solution.

In the initial latent period of this strip minimal stimuli of

I C.M. caused a subnormal contraction .
2 " " " " " .
2.5 " " " " " .
4 " " " " " .

In the pause of the strip caused by the first application of the drug stimuli of

3.5 C.M. caused a supra-normal contraction.
5 . " " " " " " .

Ventricular Muscle

Summary of the Investigations of the Condition of the Strip during Acetanilide Pause.

I, The application of acetanilide to ventricular muscle lowers both its irritability and conductivity, and to a degree in proportion to the length of time of the application of the drug.

2, The irritability and conductivity of the strip are restored in a degree proportional to the time the drug has been displaced by the normal solution.

3, It is believed that the subjection of a strip of cardiac muscle to an electrical stimulus increases to a degree, its irritability. Often a mild stimulus is enough to start a hither-to quiet strip to contracting. Gaskell(2I) speaks of a heart muscle being taught to beat. The exceptions in the preceeding tables, to the general rule, i.e. that there is continuous decrease in irritability when the strip is in the drug solution and vice versa when in the normal solution, can at least be explained partly by the sequence in which the stimuli were sent into the strip.

4, The irritability and efficiency of the strip for contraction are greater in the first pause of the strip during the application of the drug than during the latent period before the development of rhythmic contractions.

The Action of Antipyrine on the Contractions of Ventricular Muscle Strips.

The action of antipyrine in the weaker solutions on the contracting ventricular strips is a stimulating one and is indicative of the results to follow upon the application of stronger solutions. There always occurs a stimulation manifest in the amplitude of the contracting strip to which it is applied in .1 and .2 percents. This increase in amplitude is accompanied by no change or by a more or less compensatory decrease in rhythm.

Stronger percentages of antipyrine, .5 to .8 percents approach nearer being the percents affording maximal stimulation. In addition to stimulating the strip as to the amplitude, ~~its efficiency~~ there is gr greater stimulation manifest if the rhythm in 59 percent of the cases. In the others there is merely maintenance of normal rhythm.

There is not evidence of a cumulative action of antipyrine in a succession of applications to the same strip. There does seem to be, however, in most cases in tables I to 4, a tendency toward increased action as the individual bath of antipyrine is prolonged.

The first evidence of toxicity is seen when antipyrine is applied to the ventricular strip in 1. percent solution. There is a slight depression of rhythm which is more than compensated for by the unfailing accompanying increase in amplitude. If the exposure of the strip to the drug solution is prolonged to two or more minutes, there is a progressively greater decrease in the amount of stimulation evident in the strip in each case. The same characteristic increase in tone which marks the action of toxic percentages of acetanilide , when applied to a ventricular strip

is manifest also when I. percent of antipyrine is used on the strip.

There is not any doubt as to the toxicity of antipyrine in 2. percent solution. The tone in each case is greatly increased. There is initial depression shown upon the first application to the strip. The depression is increased as the application of the drug is prolonged and is accompanied by a great increase in tone. A suggestion of a cumulative action of antipyrine from one application to another, is seen in the successively longer periods of recovery.

Tables I and II showingg the effects of .I and .2 percent of antipyrine on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Table I

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate stated as percents of the normals after a given number of minutes. Time,	Amp.	Rate, -- Time,	Amp.	Rate.	Notes.
I4	I	3.3	.I	I	Io3	73	3	II5	73	
I4	2	3.5	.I	"	Io5	96	3	Io7	96	Decrease in tone 55 percent of normal.

Table II

I4	3	3.2	.2	"	II2	85	3	II2	95	
I4	4	I.5	.2							
I4	4	I.5	.2	"	Io6	95	I.5	Io6	92	
I5	I	I.25	.2	"	IIo	I4o	- - - - - - - -			-Lost.
I5	2	3.2	.2	"	Io2	Ioo	3	Ioo	Ioo	
I5	3	3.3	.2	"	Io3	Ioo	3	II3	96	
I5	4	3.2	.2	"	Io6	Ioo	3	II3	96	
I5	5	3.2	.2	"	Io9	83	3	Io9	93	

Table III showing the effects of .5 percent antipyrine on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp: in mins	Percent of drug.	Amplitude and rate stated as percents of the normals after a given number of minutes. Time,	Amp.	Rate.-- Time	Amp.	Rate.	Notes.
Io	3	3	.5	I	Io4	Ioo	3	Io9	Io7	Normal amplitude and rate resumed after removal of the drug.
Io	4	8	.5	"	Io4	II4	7	Io2	II7	
Io	5	2.I	.5	"	Io4	I5o	2	Io4	I5o	
Io	9	4	.5	"	Io3	I66	3.5	Io3	I66	
Io	Io	5	.5	"	Io5	Ioo	4.5	IIo	83	
I4	5	2.2	.5	"	Io5	I26	2	9o	I26	
I5	6	7	.5	"	Io9	I25	6.5	I24	9I	
I6	I	4.I	.5	"	Io4	Ioo	4	II3	Ioo	
I6	2	I.5	.5	"	Io6	Ioo	I.4	II4	75	
I7	I	6	.5	"	IoI	Io8	5	II2	9o	
I7	2	4	.5	"	Io2	Ioo	3.5	Io2	Ioo	
I7	3	2.5	.5	"	Io3	III	2.2	Io3	I25	

Table IV showing the effects of .8 percent of antipyrine on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins	Percent of drug	Amplitude and rate stated as percents of the normal after a given number of minutes. Time,	Amp.	Rate.	-- Time	Amp.	Rate.	Notes.
Io	I2	5.5	.8	I	I20	II4	5	I48	Ioo	
Io	I3	5.5	.8	"	I2I	96	4.5	I23	Ioo	
Io	I4	5.5	.8	"	Io8	III	5	II4	I2o	
Io	I6	7	.8	"	Io6	I34	6	IIo	I49	
Io	I9	3	.8	"	Ioo	I25	2.5	Io6	I25	

Tables V and VI showing the effects of I. and 2. percents of antipyrine on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured asx percents of normal.

Table V

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate stated as percents of the normal after a given number of minutes. Time,	Amp.	Rate.-- Time,	Amp.	Rate	Notes.
Io	I	I.8	I.	I	I26	64	I.5	I42	68	
I7	4	4.75	I.	"	Io8	Ioo	4.5	I27	6o	Slight irregularities in rate in 4th minute . Increase in tone II6 percent of normal.
I7	5	5	I.	"	Io8	8o	4.5	9I	86	Increase in tone I36 percent.
I7b	I	2	I.	"	Io3	II7	I.75	Io6	IIo	Increase in tone Io2 percent.
I7b	3	2	I.	"	Io2	I25	I.75	Io4	Ioo	Increase in tone Io3 percent.
I7b	4	I.75	I.	"	Io5	Ioo	I.5	Io8	Ioo	

Table VI

I7	6	25	2.	"	9o	95	5	47	II7	Increase in tone 226 percent.
						Same-	-Ie -	I4	I25	No recovery in Ringer and serum.
I7b	5	3	2.	"	97	II7	2.5	9o	94	Normal amplitude and rate attained in 5 minutes. Tone increased 226 percent of normal.
I7b	6	I6	2.	"	89	Ioo	II	I2	Ioo	No recovery. Tone increase 58o percent of normal.

The Action of Antipyrine on Contracting Sinus Strips.

Antipyrine in .I and .2 percent solutions depress the tone waves and the fundamental contractions, when shown , especially as to their rates and also the general tone. The amplitude of the tone waves and that of the fundamental contractions may or may not partially compensate for this decrease in their rates.

A suggestion of a cumulative action of antipyrine is seen in the extended periods of recovery following the successive periods of application of the drug

The increased toxicity of the higher percents(.5, .8 and I.), is marked by the lengthened time and lessened degree of the recovery of the strip as well as by the greater depression shown by the tone waves and the general tone.

Table I showing the effects of .I percent of antipyrine on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution

The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate of tone waves during the experiment stated as percents of the normal. Amp.	Rate.	General tone stated in percents of normal.	Notes.
I4	I	3.3	.I	62	6o	Io5	Recovery of tone waves in I.5 minutes. General tone 95 percent of normal.
Fundamental contractions							
after I minute.--------				Io6	7o		
" 3 "				I33	6o		
I4	2	3.5	.I	5o	5o	IoI	Recovery of tone waves in 2 minutes. General tone 96 percent of normal.
Fundamental contractions							
after I minute - ------				I33	8o		
" 3 "				I33	6o		

Table II showing the effects of .2 percent of antipyrine on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate of tone waves during the experiment stated as percents of the normal. Amp.	Rate	General tone stated in percents of normal.	Notes.
I5	I	I.25	.2	I6o	66	97	Recovery of tone waves immediately. General tone 97 percent of normal.
I5	2	3.2	.2	8o	Ioo	Ioo	Recovery of tone waves in I.5 minutes. General tone 7o percent of normal. Fundamental contractions appeared during the bath.
I5	3	3.3	.2	II4	5o	99	Recovery of tone waves 4 minutes after the bath. General tone 94 percent of normal.
I5	4	3.2	.2	8o	35	87	Recovery of tone waves in 4 minutes. General tone 84 percent of normal Fundamental contractions appeared during the bath.
I5	5	3.2	.2	IIo	4o	88	Recovery of tone waves immediately. General tone 77 percent of normal. Fundamental contractions appeared during the bath.
I4	3	3.2	.2	75	46	93	Recovery of tone waves immediately. General tone 85 percent of normal.
Fundamental contractions appear after after I minute----				----5o	Ioo		
I4	4	I.5	.2	5o	I5o	Io3	Recovery of tone waves in I minute. General tone Io7 percent of normal

Fundamental contractions not measurable, they died out when the application of the drug began.

Table III showing the effects of .5 percent solution of antipyrine on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Per-cent of drug	Amplitude and rate of tone waves during the experiment stated as percents of the normal		General tone stated in percents of normal.	Notes.
				Amp.	Rate.		
Io	3	3	.5	3o	I42	65	Recovery of tone waves in I.5. General tone 77 percent of normal.
Io	4	8	.5	52	75	98	Recovery of tone waves in 2 minutes, (a Ringer plus serum bath preceeded the normal of this).
Io	5	2.I	.5	8	Ioo	63	No recovery of tone waves till after the use of Ringer's solution. General tone 2I percent of normal.
Io	9	4	.5	Io5	33	78	Recovery of tone waves at once. General tone 4I percent of normal.
Io	Io	5	.5	o	o	3I	Recovery of tone wave 6 minutes later. General tone Io8 percent of normal
I5	6	7	.5	I33	I6	94	No recovery of tone waves. General tone 92 percent of normal. Fundamental contractions occured during and after the bath.
I7	I	6	.5	88	83	89	No recovery of tone waves till after several baths of the normal solution. General tone 83 percent of normal.
I4	5	2.2	.5	8o	5o	83	Recovery of tone waves in I minute. General tone 68 percent of normal.

Tables IV and V showing the effects of .8 and I. percents of antipyrine on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Per cent of drug	Amplitude and rate of tone waves during the experiment stated as percents of the normal. Amp.	Rate.	General tone stated in percents of normal.	Notes.
Table IV.							
Io	I2	5.5	.8	o	o	7I	No recovery of tone waves or general tone till I2 minutes of Ringer bath.
Io	I3	5.5	.8	o	o	73	No recovery of tone waves or general tone until after I3 minutes of Ringer bath.
Io	I4	5.5	.8	o	o	86	No recovery till a after 43 minutes of Ringer and of NaCl baths.
Io	I6	7	.8	Io	2o	6o	No recovery in 3o minutes.
Table V.							
Io	I	I.8	I.	Ioo	25	65	General tone recovered after a Ringer bath.

The fundamental contraction grew larger as the general tone decreased

Summary of the Action of Antipyrine on Contracting Heart Strips.

I, Antipyrine is not without effect when applied to ventricular and sinus strips .

2, The stimulation of the ventricular strip shown upon the application of .I and .2 percent is submaximal. It falls only upon the amplitude. There may be a compensatory decrease in rate.

3, The maximal stimulation of the strip occurs when .5 and .8 percents of antipyrine are applied to the strip. The stimulation is always shown in the amplitude and may be manifest in the rate.

4, Depression is evident upon the application of 1. percent antipyrine to the strip. It is shown first in the rate then as the application is prolonged, it is evident in the amplitude.

5, The sinus is more susceptible to the action of antipyrine and is depressedby it in percentages that afford only submaximal stimulation to the ventricular strip.

6, The toxic percentages produce the same striking and characteristic increase in tone that is seen when a toxic solution of acetanilide is used.

7, There seems to be no certain cumulative action of antipyrine in a series of applications to one strip. Although the longer a single application of the drug is continued the longer will be its period of recovery, and usually the less complete it will be.

The Action of Acetphenetidin on Contracting Ventricular Strips.

The action of acetphenetidin, in the weaker solutions, exp. I8 and I8b, on contracting ventricular strips is a stimulating one, the stimulation falling on either the amplitude or rate. There is never an entirely compensating decrease in the one for the increase in the other.

Acetphenetidin is only sparingly soluble. A saturate solution contains one part in nine hundred and twenty five parts of water(28), making a solution of .Io8 percent.

A saturate solution of this drug is stimulating in 8o percent of the cases in which it is applied to the ventricular strip. The stimulation falls principally upon the amplitude. Since , with one exception, the 2o percent of the cases in which the saturate solution of acetphenetidin fails to stimulate but causes an initial depression followed by further depression, occur consistently in one and the same experiment; since no deviations from this result are seen through-out the series of experiments on this one strip, and since the same solutions are used one may justly suspect the vitality of the strip.

There seems to be no signs of an accumulative effect in a succession of experiments. There is a decrease from the initial stimulation in an individual applicaation of the drug, if it is prolonged over 2.8 minutes.

The margin between the strength of the coal tar drugs that stimulates and that depresses is a slight one. Moreover, as has been seen before, there is a probability that the relative toxicity of a certain percent solution of the drugs is dependent more or less upon the vitality of the strip to which it is applied.

Tables I and II showing the action of .o4 and .o6 percents of acetphenetidin on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Table I.

Exp. No.	Trial No.	Duration of exp. in mins.	Per-cent of drug	Amplitude and rate stated as percents of the normal after a given number of minutes. Time,	Amp.	Rate.	Time	Amp.	Rate.	Notes.
I8b	I	5.25	.o4	I	Ioo	Io7	5	8o	I45	Slight irregularities in rhythm occured in the 3rd and 5th minutes.
I8b	2	3.75	.o4	"	Ioo	Io8	3.5	Ioo	Io8	
I8	I	6.25	.o4	"	95	I94	6	78	I7I	Increase in tone I42 percent of normal. No recovery of amplitude.
I8	2	6	.o4	"	Io3	Ioo	5.5	83	66	

Table II.

I8	3	6.75	.o4	"	Ioo	II2	6	88	I56	Slight irregularities due to quickening, occur periodically.

Table III showing the effects of a saturate solution of acetphenetidin on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug.	Amplitude and rate stated as percents of the normal after a given number of minutes. Time,	Amp.	Rate.	— Time,	Amp.	Rate.	Notes.
2I	I	3	Sat.Sol.	I	98	2I7	2.75	IoI	227	Contractions stopped 5 minutes after the drug was removed. Recovery 6 minutes later. General tone 94 percent.
2I	2	3.75	"	"	Ioo	Io8	3.5	95	Io8	Irregularities in amplitude and rhythm after removal of the drug.
2Ib	I	I.8	"	"	II3	Ioo	I.5	II7	86	The increase in amplitude lasted 4 minutes after the bath. General tone 78 percent of normal.
2Ib	2	2.9	"	"	Io2	I2o	2.5	97	I25	Stimulation stopped upon removal of the drug and fell below normal.
2Ib	3	2.2	"	"	Io4	99	2	Ioo	II8	" " " " " ".
2Ib	4	4	"	"	Io8	III	3	Ioo	II6	Irregularities in both the amplitude and rate occured in the 4 th minute. They disappeared upon the removal of the drug.
2Ib	5	4.7	"	"	III	96	4.5	94	84	Decrease in amplitude right after the removal of the drug.

Table III, continued, showing the effects of a saturate solution of acetphenetidin on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate stated as percents of the normal after a given number of minutes. Time,	Amp.	Rate --	Time	Amp.	Rate.	Notes.
2Ib	6	2.4	Sat.Sol.	I	Io9	I2o	2.2	Ioo	I25	Decrease in amplitude just after the bath. Increase in tone I25 percent.
2Ib	8	4	"	"	I23	Io7	3.5	I3o	29	Normal rhythm was resumed 9 minutes after the drug was removed. Increase in tone I58 percent.
2Ib	9	2.4	"	"	II5	87	2.2	I42	62	Normal rhythm was resumed I minute after the bath.
22	I	2.5	"	"	II6	93	2.2	I2o	Ioo	
22b	I	2.8	"	"	II3	Io4	2.5	I26	96	
22b	2	I.6	"	"	Io7	Io4	I.5	II7	Ioo	
23	I	3.2	"	"	I35	75	3	I5o	75	Slight irregularities in amplitude occured.
23	2	2.7	"	"	I22	72	2.5	I26	66	Stimulation ceased when the drug was removed.
23	3	4.3	"	"	I3o	Ioo	3	Ioo	I23	Resumption of normal amplitude and rate.

Table III, continued, showing the effects of a saturate solution of acetphenetidin on the amplitude and rate of a strip of terrapin's ventricle contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp' in mins.	Percent of drug.	Amplitude and rate stated as percents of the normal after a given number of minutes. Time	Amp.	Rate.	Time.	Amp.	Rate.	Notes.
23b	2	3.8	Sat.Sol.	I	I2I	Ioo	3.5	I3o	8o	
2o	I	3.8	"	"	Io4	83	3	Io7	66	Contractions stopped at the end of 3 minutes and were not resumed until 3.5 minutes after the bath.
2o	2	5	"	"	Io2	9o	4.5	Io6	22	Irregularities in rate occured until removal of the drug.
2o	3	3.75	"	"	Io4	9I	3.5	Io2	7I	" " " ".
2o	4	6.2	"	"	Io6	92	6	5I	92	Irregularities in both amplitude and rate occured till removal of the drug.

The Action of Acetphenetidin on Contracting Sinus Strips.

Acetphenetidin in the weaker solutions may or may not cause a depression which falls just upon the rhythm usually. The time of recovery is prolonged and less com;lete as the succession of applications of the drug follow each other.

A saturate solution of Acetphenetidin applied to the sinus strip, depresses it in rhythm or in amplitude or in both. The degree and the time of recovery are scarcely less complete and prolonged following the use of the saturate solution than following the use of .o4 and .o6 percents of acetphenetidin.

Tables I and II showing the effects of .o4 and .o6 percents of acetphenetidin on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate of tone waves during the experiment stated as percents of the normal. Amp.	Rate.	General tone stated in percents of normal.	Notes.
I8b	I	5.25	.o4	Ioo	95	92	Recovery immediately.
I8b	2	5.75	.o4	I25	Ioo	IoI	Recovery immediately.
I8	I	6.75	.o4	II2	IIo	83	Fairly good recovery of tone waves immediately. Recovery of general tone 9o percent.
I8	2	6	.o4	Ioo	66	8o	Immediate recovery of tone waves. General tone 73 percent.

Table II.

I8	3	6.75	.o6	76	66	87	No recovery of tone waves for 6 minutes Recovery of general tone 58 percent of normal.

Table III showing the effects of a saturate solution of acetphenetidin on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Percent of drug	Amplitude and rate of tone waves during the experiment stated as percents of the normal. Amp.	Rate.	General tone stated in percents of normal.	Notes.
2I	I	4.5	Sat.Sol.	I56	Io6	84	Recovery of tone waves immediately. Recovery of general tone 67 percent.
2I	2	3	"	I43	66	Io2	Recovery of tone waves immediately, waves larger and slower. General tone 85 percent of normal. General tone 85 percent of normal.
2I	3	3.75	"	—	5o	9o	Recovery of tone waves 3 minutes after the bath. General tone 74 percent of normal.
22	I	2.8	"	9I	83	Ioo	Recovery of tone waves immediately. General tone Ioo percent of normal.
22	2	I.6	"	—	—	95	Tone waves recovered immediately. General tone 9 percent of normal.
23	2	2.7	"	47	Io9	87	Tone waves recovered in 2 minutes after the bath. General tone 6Ipercent of normal.
23	3	3.2	"	59	I2o	67	

Summary of the Action of Acetphenetidin on Ventricular and Sinus Strips.

There is every reason to believe that the percent of acetphenetidin affording maximal stimulation to the ventricular strip, corresponding to .5 and .8 percent antipyrine and .04 and .05 percents of acetanilide is not reached because of its being so sparingly soluble.

Equally good evidence that acetphenetidin reaches its limit of solubility before it reaches the strength affording maximum stimulation to the ventricular strip is that the saturate solution of it does not cause great depression of the sinus strip. It is a rule in the experiments with acetanilide and antipyrine that the strength of the drug that affords maximal stimulation to the ventricular strip unfailingly causes very great depression of the sinus /

The Effects of Hypertonicity of a Solution on the Amplitude and Rate of the Contractions of Ventricular and Sinus Heart Strips.

Carlson (29) thinks that there appears to be an unwarranted, tacit assumption on the part of pharmacologists that the osmotic pressure change, due to the solution of a drug in the blood, is a negligible factor in the action of the drug on the heart.

In experimental work on the limulus heart , he found that hypertonicity of the medium used depressed the rhythm primarily. In the case of the tortoise auricle, hypertonicity of the bathing solution depressed the amplitude of the auricular beats, usually without altering the rhythm. If the rate were altered it was invariably in the direction of retardation. The tone rhythm was also depressed in case it was present shown.

Eyster and Wilde(3o) found that hypertonic solution of Ringer plus sodium chloride or glucose caused stimulation of the sino-auricular strips of the frog and terrapin. In further experiments made on mammals, it was evident that hypertonic solutions of sodium chloride or glucose, in moderate doses,caused an initial increase in cardiac output. Very large doses of this hypertonic solution caused a decrease in cardiac output.

In order to estimate how much , if any, the resulting effects obtained in the foregoing experiments might be due to the increased osmotic pressure of the solution ,experiments were made on the action of hypertonic salt solutions on the heart strips. The results are shown in the following tables.

Table I showing the effects of a hypertonic solution, I percent of sodium chloride on the amplitude and rate of a strip of terrapin's ventricle. The pesults are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Amplitude and rate stated as percents of the normal after a given number of minutes. Time,	Amp.	Rate.	Time,	Amp.	Rate.	Notes.
53	I	7	I.5	Io2	Io4	6	Io4	Io4	
53	2	II	"	94	II5	Io	77	I2o	
53	3	2	"	9I	I2o				
53b	I	5.6	"	Ioo	I23	5	Io9	I23	
53b	2	8	"	Ioo	Io4	7	Io5	Io4	
53b	3	9	"	Io3	II4	8	87	II4	
53b	4	5	"	93	I2o	4	88	I2o	
53b	5	II.5	"	88	III	Io	47	I22	Typical NaCl tracing.

Table I showing the effects of a hypertonic solution, I. percent of sodium chloride on the amplitude and rate of a terrapin's sinus contracting in Ringer's solution. The results are figured as percents of normal.

Exp. No.	Trial No.	Duration of exp. in mins.	Amplitude and rate of tone waves during the experiment stated as percents of the normal. Amp.	Rate	General tone stated in percents of normal.	Notes.
53b	I	5.66	63	92	8o	Fundamental contractions greater after NaCl I. percent was removed.
53b	2	8.	I4o	Io6	II6	
53b	3	9	Io6	Io6	IIo	Fundamental contractions greater during the bath of I. percent NaCl.
53b	4	5	I5o	I25	97	No fundamental contractions shown.
53b	5	II.5	53	I24	83	No fundamental contractions shown.

Results and Summary of the Effects of Hypertonicity on Contracting Heart Strips.

In the experiments tabulated in the preceeding tables .7 percent of sodium chloride was used for the normal solution. The difference in the osmotic pressures of this normal and and the I. percent hypertonic solution is about 2 atmospheres. The difference in the in the osmotic pressures of the solution used as normal, and the normal plus the greatest percent of any of the drugs used,(2. percent antipyrine) is about 2.2 atmospheres. So the hypertonicity in the test case nearly approaches in degree , the case of much the greatest hypertonicity of the drug solutions.

As is seen in the preceeding tables this hypertonic sodium chloride solution stimulates the strips in 86 percent of the applications made. It depresses only slightly in 9 percent of the remaining cases. On the other hand all the drug solutions affording the greatest amount of hypertonicity cause greater or less depression without exception. Consequently one may conclude that the results,obtained in these experiments,are results due to the action of the drug and that the increased osmotic pressure of the drug solution over the normal rather than adding to and acentuating the depressing action of the drug may counteract its influence to a degree, by a stimulating ac
action.

The factor of hypertonicity in the weaker solutions,i.e. .oI to .o5 percents of acetanilide and .o4 and .o6 percents of acetphenetidin, may or may not increase the stimulating action of these drugs in these percents. If it does the influence must be infintesimal. It is more probable that the hypertonicity of the stimulating percents ,.5 and .8, of antipyrine may contribute to the stimulating action on the strip.

Summary in General.

I, The relative toxicity of the drugs to cardiac muscle is in the order named; acetanilide, antipyrine, acetphenetidin.

2, Acetanilide acts on the ventricular strip by stimulating slightly, stimulating to a maximal degree, or depresses greatly according to the strength of the solution.

3, The action of acetanilide on the sinus strip is marked by varying degrees of depression according to the strength of the drug used.

4, Antipyrine stimulates or depresses the ventricular strip to which it is applied in degrees varying with the percent.

6, The sinus is depressed throughout by antipyrine, from the weakest to the strongest solution used.

7, The application of toxic solutions of acetanilide and antipyrine causes a characteristic and great increase in tone of the ventricular strip.

8, The longer the exposure of the strips of heart muscle to acetanilide and antipyrine the longer and the less complete is the period of recovery following.

9, The depression of the heart strips following the application of the drugs appears to be due to lowered conductivity and irritability.

Io, The general action of acetphenetidin on heart strips corresponds to that of antipyrine but it is less in degree.

II, The sparing solubility prevents further investigation of its (antipyrine) action on the heart strip.

I2, There is no certain evidence that the drugs are cumulative in their action. Probably a slight tolerance is developed on the part of the strips, to the drugs after repeated exposure to them.

I3, Lingle's theory of tone is supported.

I4 The factor of hypertonicity, caused by the addition of the drugs in the greater percents to the normal solutions, has no positive influence on the resulting depression of the strips. The weaker percents of the drug may have their stimulating influence increased very slightly by this factor of hypertonocity.

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