The physiological action of drugs : an introduction to practical pharmacology / by M. S. Pembrey, and C. D. F. Phillips.

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AN INTRODUCTION TO PRACTICAL PHARMACOLOGY

BY

M. S. PEMBREY, M.A., M.D.

JOINT-LECTURER ON PHYSIOLOGY IN GUY'S HOSPITAL MEDICAL SCHOOL

AND

C. D. F. PHILLIPS, M.D., LL.D.

EXAMINER IN MATERIA MEDICA AND THERAPEUTICS IN THE UNIVERSITY OF ABERDEEN;
LATE EXAMINER IN THE UNIVERSITIES OF EDINBURGH AND GLASGOW

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EDWARD ARNOLD

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PREFACE

THE experiments described in this elementary work have been made as simple as possible, so that they may be performed by a medical student. For a similar reason they have been limited to those operations which can be performed upon a brainless frog. The law relating to experiments on animals renders necessary the destruction of the animal's cerebral hemispheres.

It is hoped that this small work may be of some value as a contribution to the knowledge of the physiological action of drugs. The results of the experiments are based upon numerous observations and graphic records; the drugs have been dissolved in normal tap-water saline solution, and, for the determination of the poisonous effects, have been administered by hypodermic injection under the skin of the back. The tracings are portions of continuous records, and have been checked by control experiments.

We wish to thank Professor Stockman, Dr. Dixon, Dr. Beddard, and Mr. Leonard Hill for reading through the proofs and for some valuable suggestions.

CONTENTS

INTRODUCTORY EXPERIMENTS

PHYSIOLOGICAL ACTION OF DRUGS

INTRODUCTORY EXPERIMENTS

THE following directions for the dissection and preparation of various portions of the frog's body and the performance thereon of some simple experiments will serve as an introduction to the main purpose of this work—the study of the action of drugs. It is necessary that a knowledge of the normal should precede the investigation of the changes introduced by the action of a drug.

The law relating to experiments on animals renders necessary the destruction of the animal's cerebral hemispheres, and thus limits the experiments, which can be properly performed by a student, to observations upon frogs. Even apart from this legal obligation, there is one great advantage in the selection of this animal. The various tissues of a cold-blooded animal, such as the frog, retain their individual vitality for hours after the death of the animal, and are thus most suitable for experiments.

EXPERIMENT I.—*Complete Destruction of the Central Nervous System.*—The articulation of the head of the frog with the vertebral column can be readily felt with the finger. At this point the skin and other tissues should be rapidly pierced, and the brain destroyed by the insertion of a probe or a blanket-pin. If, after this operation, the eye be touched with the finger, the eyelid is not closed—the "corneal reflex" has been abolished.

The probe is now pushed down the spinal cord, and convulsive movements of the limbs will be observed; these are due to the impulses sent down the motor nerves, when the

nerve-cells are stimulated in the process of destruction. The contractions quickly cease, and now no reflex movements can be obtained in any part of the body.

In experiments in which it is desirable to prevent any loss of blood, the cerebral hemispheres can be destroyed by quickly compressing the skull between the blades of a pair of Spencer Wells forceps.

Experiment II.—*Dissection of a Muscle and Nerve Preparation.*—The frog used in the last experiment is placed belly downwards and pins are fixed through the feet. The skin around the ankle is divided and the tendo Achillis is exposed, and a thread[1] is passed under the tendon and tied just above the sesamoid bone; the tendon is then divided below the sesamoid bone. The tendon and its muscle, the gastrocnemius,

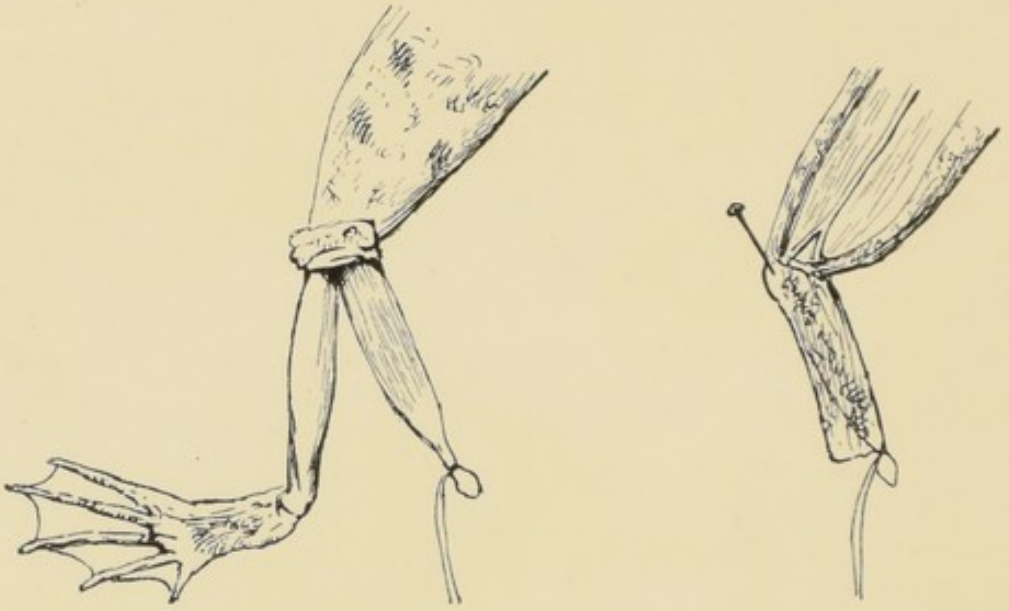


Fig. 1. Fig. 2.

Diagrams of a Muscle and Nerve Preparation.

Fig. 1.—The first stage of dissection.

Fig. 2.—The second stage of dissection. The sciatic nerve exposed and the gastrocnemius muscle covered by skin.

are pulled upwards and carry with them the skin; the bone of the leg and the remaining muscles are removed by a cut

[1] A simple aneurism needle can be made by fixing a needle with a large eye into a pen-holder.

below the knee-joint, and the gastrocnemius muscle is protected from drying and contact with foreign substances by drawing down the "trowser" of skin. The skin over the posterior surface of the thigh is next divided by a longitudinal incision in the mid-line; the muscles are separated, and the sciatic nerve is dissected up to its exit from the vertebral column, a small piece of which is bisected and cut away with the nerve. A pin is pushed through the lower extremity of the femur, and the thigh is severed from the body by a cut close to the articulation of the head of the femur. The nerve[1] is allowed to lie among the muscles until it is required for stimulation; the lymph of the muscles keeps the nerve moist, and thus preserves its excitability.

EXPERIMENT III.—*Single Muscular Twitch—Direct and Indirect Stimulation.*—The last dissection is used for this experiment. The sciatic nerve is raised from between the muscles of the thigh, and is laid upon a pair of electrodes. A very weak induction-shock is passed; the muscle does not contract. The strength of the induction-current is gradually increased until a twitch of the muscle is observed; this is a *minimal* stimulus. After steadily increasing the strength of the stimulus, a point is reached at which the greatest contraction is observed, and further augmentation of the stimulus leads to no increase in the contraction of the muscle; this is the *maximal* stimulus for *indirect* stimulation of the muscle by means of its nerve.

The electrodes are now applied *directly* to the muscle and the experiment is repeated. It will be found that the stimulus required for the muscle is stronger, proving that the *excitability of nerve is greater than that of muscle.*

This difference in the excitability of muscle and nerve can be measured approximately by noting the distance of the secondary from the primary coil of the inductorium when

[1] The nerve should not be pinched, but should be lifted by the piece of the vertebral column.

the minimal and maximal points are determined. The following figures give the results of such a measurement.

Nature of Induction Shock.	Nerve.		Muscle.	
	Minimal. cm.	Maximal. cm.	Minimal. cm.	Maximal. cm.
Make	39	7	20	5
Break	48	10	30	7

The table shows, moreover, that the break-induction-shock is a more effective stimulus than the make; this is due to the greater strength and more rapid rise in the intensity of the break-shock. In comparative estimations of the excitability of a tissue it is therefore necessary to use only the make or only the break-shocks.

The determination of the strength of the minimal stimulus for a muscle or nerve serves as a gauge of the excitability of those tissues under different conditions, and in this way the effect of drugs upon muscle and nerve can be studied.

EXPERIMENT IV.—*Preparation of the Heart and the Vago-Sympathetic Nerve—Inhibition of the Heart by Stimulation of the Vagus; Acceleration by Stimulation of the Sympathetic.*—A pithed frog is placed on its back, and, by a median incision of the skin, the sternum and floor of the mouth are exposed; the flaps of skin are removed on each side, and then the sternum is carefully cut away without any damage to the heart. The pericardium is slit open and the beating heart is exposed. The contraction of the sinus venosus is followed by that of the two auricles and of the single ventricle, which is in turn succeeded by the pulsation of the truncus arteriosus. The chambers of the heart

FIG. 3.

FIG. 4.[1]

Diagrams of the frog's heart. A. Anterior view. B. Posterior view, heart turned up. 1, ventricle; 2, left auricle; 3, right auricle; 4 and 5, aortæ coming off from truncus arteriosus; 6, frænum; 7, left superior vena cava; 8, right superior vena cava; 9, inferior vena cava.

[1] The crescentic groove which separates the sinus venosus from the auricles is indicated by the interrupted line.

during diastole are distended and flushed with blood; during systole the colour pales, the chambers become smaller and tense.

The vago-sympathetic nerve is readily exposed by the following dissection. The skin in the middle line of the back is divided and the scapula is lifted up and cut away; the fore limb is pulled outwards and removed. A finger is placed in the frog's mouth in order to place the structures of the side of the neck and the floor of the mouth on the stretch. The following nerves can now be easily seen: the thick brachial plexus, divided by the removal of the fore limb; in front of it a much smaller nerve, the hypoglossal, which passes down to the floor of the mouth; then the vago-sympathetic, which comes from the skull, and, running by the side of the carotid artery, crosses under the hypoglossal nerve; and lastly, issuing from the same foramen as the vago-sympathetic, the glosso-pharyngeal nerve, which for a short distance runs

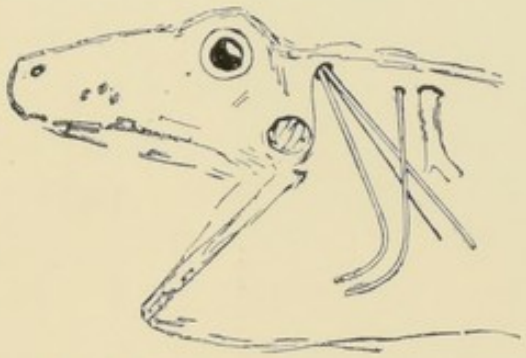


Fig. 5.—Diagram of nerves in the frog's neck.

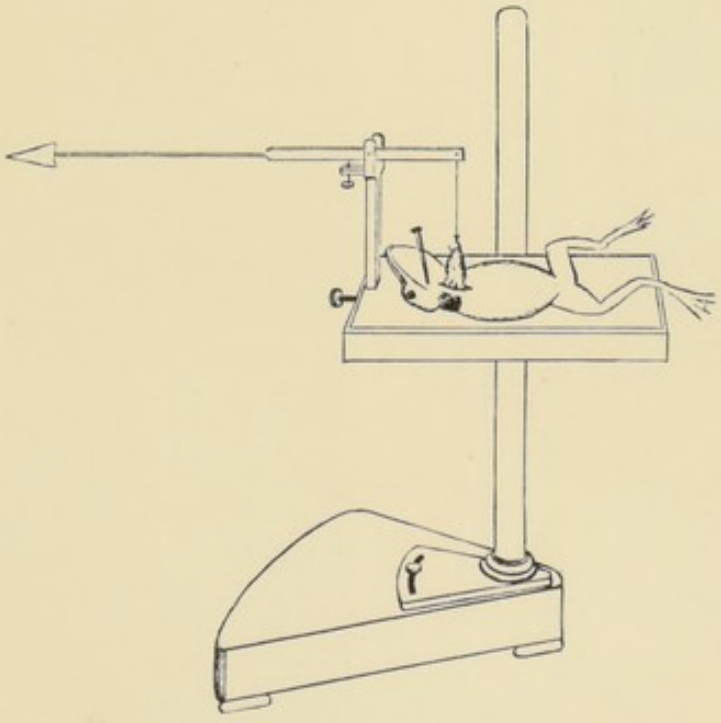


Fig. 6.—Diagram of a cardiograph.

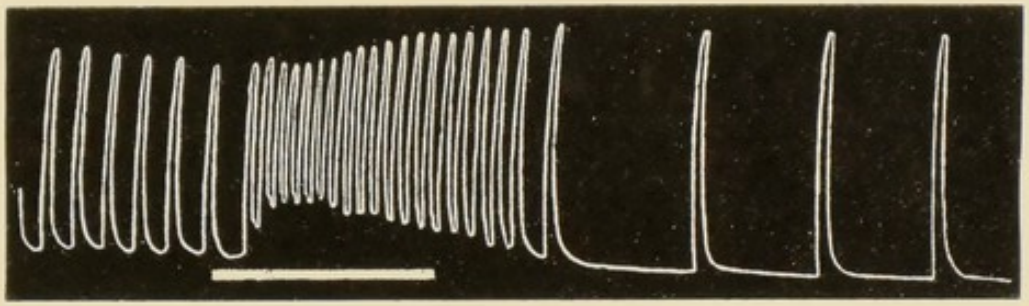


FIG. 7.[1]—Contraction of frog's heart. The effect of weak stimulation of the vago-sympathetic nerve. The white horizontal line shows the duration of stimulation. The effect does not begin at once ; there is a "latency." The heart then beats more rapidly and does not relax completely ; the acceleration persists for a few beats after the cessation of the stimulus. The "after-effect" is a much slower and a more forcible beat.

[1] All the curves in this work read from left to right.

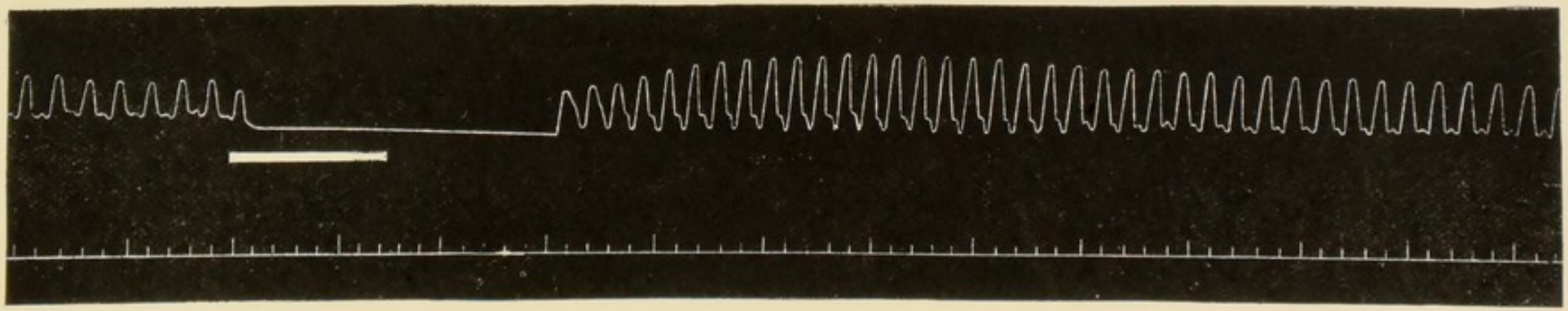


FIG. 8.—Contraction of frog's heart. The effect of stimulation of the vago-sympathetic nerve with a moderately strong faradising current. The heart was moistened with normal tap-water saline solution. The temperature of the air was 20·5°. The white horizontal line shows the duration of the stimulus ; the time-mark below indicates seconds. There is one contraction of the heart after the commencement of the stimulation ; there is a "latency." The heart then ceases to beat and remains relaxed for a few seconds after the cessation of the stimulus. It then begins to beat with gradually increased force, showing a so-called "staircase" effect ; the frequency of contraction is also increased. In a few seconds the "after-effect" passes off.

parallel with the vago-sympathetic but soon turns downwards and forwards to the floor of the mouth.

A pair of electrodes are placed under the dissected vago-sympathetic nerve and the frequency of the heart's beat is noted; a weak faradising current is passed through the nerve; the heart beats more rapidly owing to the stimulation of the sympathetic fibres of the nerve. The strength of the induction-currents is increased and the effect of the strong stimulus is excitation of the vagus; the heart stops beating in the diastolic phase.

These effects can be recorded graphically. The frog is placed on a myograph; the ventricle is supported by the tip of the finger, and a small bent pin is placed through the apex of the ventricle. A thread connects this small hook with a recording lever, as shown in the diagram (Fig. 6).

The accelerating effects of the sympathetic and the inhibitory influence of the vagus are shown by the curves (Figs. 7 and 8).

It is important to remember that the fibres of the vagus and sympathetic nerves run together, and that the pure vagus can only be stimulated inside the skull before it is joined by the sympathetic.

Experiment V.—*The Effect of Temperature upon the Contraction of Voluntary Muscle.*—The gastrocnemius muscle is prepared without a covering of skin and is attached to a myograph in the ordinary way (Fig. 9). One wire of the electrodes is fixed to the pin which passes through the lower extremity of the femur; the other wire is joined to a piece of capillary copper-wire, which has been threaded by means of a needle through the tendo Achillis. In this way the electric current can be passed through the length of the muscle, and the very fine wire will prevent any friction or obstruction to the free movement of the muscle when it contracts.

Cold tap-water saline solution,[1] which has been cooled by ice, is slowly poured upon the muscle; the temperature of the

[1] Tap-water containing 0·6 per cent of sodium chloride.

solution is noted, and the contraction produced by the passage

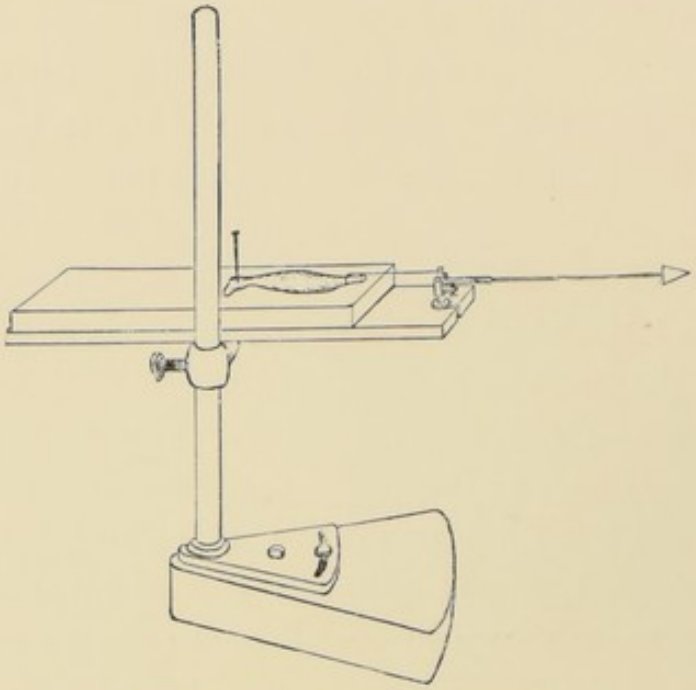


FIG. 9.—Diagram of a myograph.

of a single maximal stimulus is recorded upon a revolving

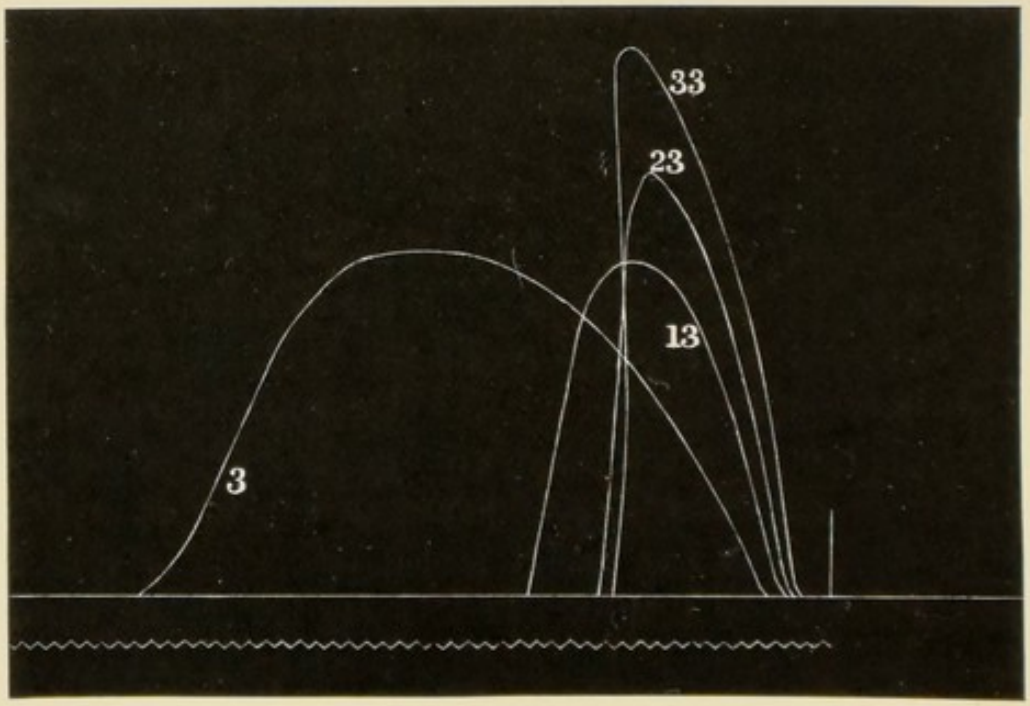


FIG. 10.—The effect of temperature upon the contraction of the gastrocnemius muscle. The time is marked in $\frac{1}{100}$ second. The tracing should be read from right to left.

cylinder covered with smoked paper. The experiment is repeated with solutions with a temperature of 13°, 23°, and

33° respectively. The contraction, it will be observed, is more rapid in its onset and of shorter duration when the muscle is exposed to a higher temperature. These points are illustrated by the curves (Fig. 10).

This method is simple and effective, but it is obvious that, if exact results be needed, the muscle must be suspended in

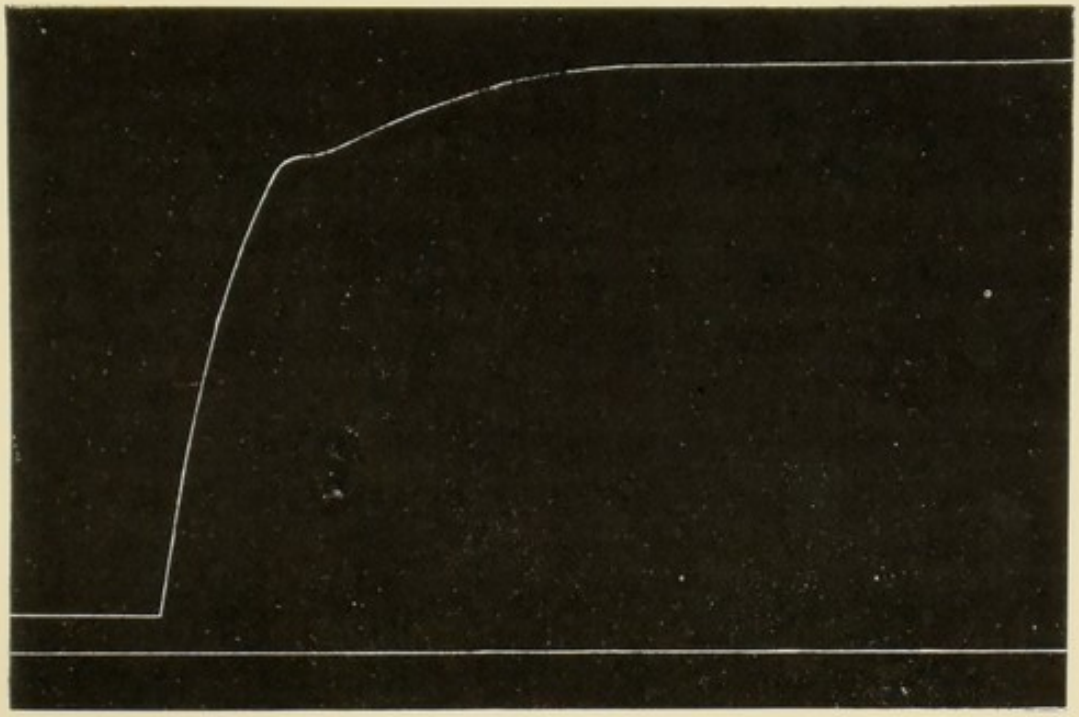


FIG. 11.—Curve of the shortening of the gastrocnemius muscle during heat-rigor.

tap-water saline solution of the given temperature, until its substance has attained that temperature.

This experiment shows that the temperature of the surroundings has a marked effect upon muscular contraction. It is important, therefore, to observe the temperature during an investigation of the action of a drug upon muscle.

On another portion of the drum is recorded the effect of saline solution heated to 50° or 60°; the muscle shortens but does not relax; it is in "heat-rigor" and will have lost its excitability. This heat-rigor depends upon the coagulation of the proteids of the muscle.

EXPERIMENT VI.—*The Effect of Temperature upon the Heart.*—A graphic record of the heart's contraction is taken,

and under the curve the time is marked in seconds; against this record is noted the temperature of the room. The effect of temperature is then observed by pouring over the heart tap-water saline solution at temperatures of 3°, 13°, 23°, 33°, and 43° respectively, and recording separately the results. A rise of temperature quickens the rate and diminishes the force and duration of the heart's contraction, as shown in the following curves (Fig. 12).

In the tracing obtained at the low temperature it will be observed that three contractions of the ventricle occur in ten seconds, and the contraction of the auricles is well shown as a slight rise preceding the systole of the ventricle. At 13° there are five ventricular contractions in ten seconds, and the contraction of the auricles occurs before the ventricle has completely relaxed; at 23° the contractions of the ventricle are six in ten seconds; the auricular contraction occurs still earlier on the down-stroke, due to the relaxation of the ventricle; at 33° the frequency of the heart-beat is increased to ten in ten seconds, and the height of the contraction is reduced to one-third of the value at 3°. When the tap-water saline solution at 43° is poured on the heart, it beats irregularly in force and rhythm. The application of the solution at 53° will stop the pulsation, and will cause the heart to pass into heat-rigor and its proteids to coagulate.

This simple method is not rigorously exact, for the warm tap-water saline solution rapidly cools and the entire mass of the cardiac muscle is not raised to the temperature of the liquid. The results, however, show clearly the influence of temperature upon the beat of the heart, and the importance of observing the temperature of the surroundings during investigations upon the heart.

EXPERIMENT VII.—*The Inhibitory Region of the Heart—Stannius' Experiment.*—The heart of a pithed frog is exposed, and a thread is tied to the frænum, a slip of pericardium which passes from the posterior wall of the pericardium to the

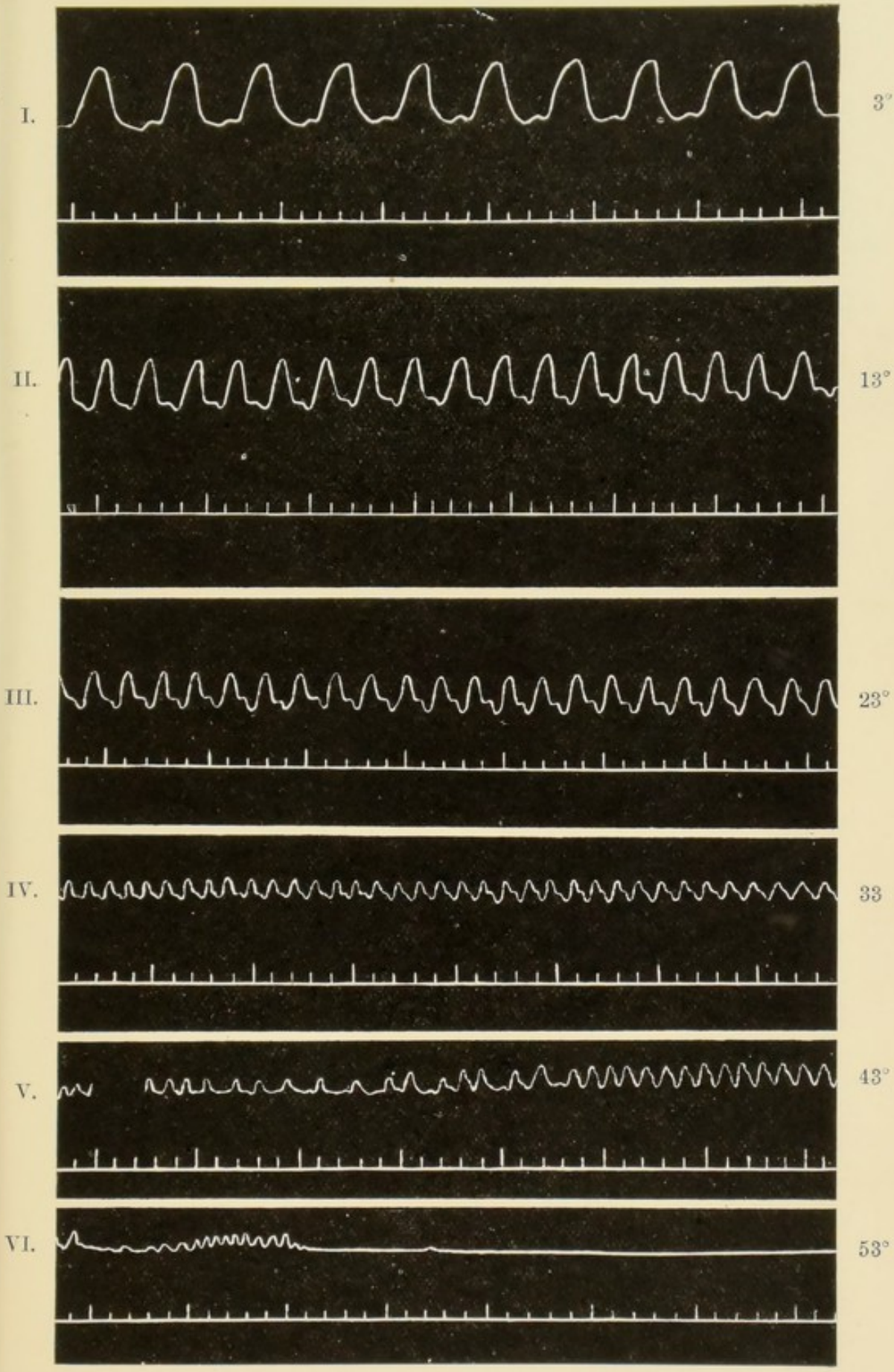


FIG. 12.—Curves showing the effect of temperature upon the contraction of the frog's heart. The time is marked in seconds.

posterior surface of the ventricle (Fig. 4). The attachment of the frænum to the pericardium is cut, and the heart is pulled upwards, so that its posterior surface is well exposed. At the junction of the sinus with the right auricle will be seen a crescentic groove, known as the *inhibitory region* of the heart. To this point electrodes are applied, and it will be found that the passage of a faradising current through this portion of the heart will cause it to cease beating during, and for a short time after, the stimulus. In the inhibitory region are found a plexus of the cardiac nerves and ganglion cells.[1]

Stannius' Experiment.—By means of a large-eyed needle, a thread is passed under the two aortæ just above the truncus arteriosus; the heart is pulled towards the mouth by means of the ligature upon the frænum, and then the thread is tied tightly round the junction of the auricles with the sinus venosus. The beat of the auricles and ventricle ceases, but that of the sinus venosus continues.

By this "Stannius' ligature" the contractions of the auricles and ventricle can be suspended for a considerable time, and the cardiac muscle in a quiescent condition can be used for experiments.

Experiment VIII.— *The Cardiac Plethysmograph.*—For the investigation of the action of drugs upon the heart, the passage of the drug, dissolved in blood or some innocuous fluid, through the heart is often desirable, for thereby the drug is brought into intimate contact with the tissues of the heart. Schäfer's cardiac plethysmograph (Fig. 13) may be used for this purpose.

There are, however, considerable disadvantages attached to this method. Much practice is necessary in the somewhat difficult manipulation. The heart is easily injured, and, owing to the ligature around its base, it is impossible to investigate the influence of drugs upon the cardiac nerves. It is in fact a preparation of the ventricle. In this series of experiments

[1] See p. 97.

the simple method of application of the drug to the outside of the heart will be employed; the manipulations are easier,

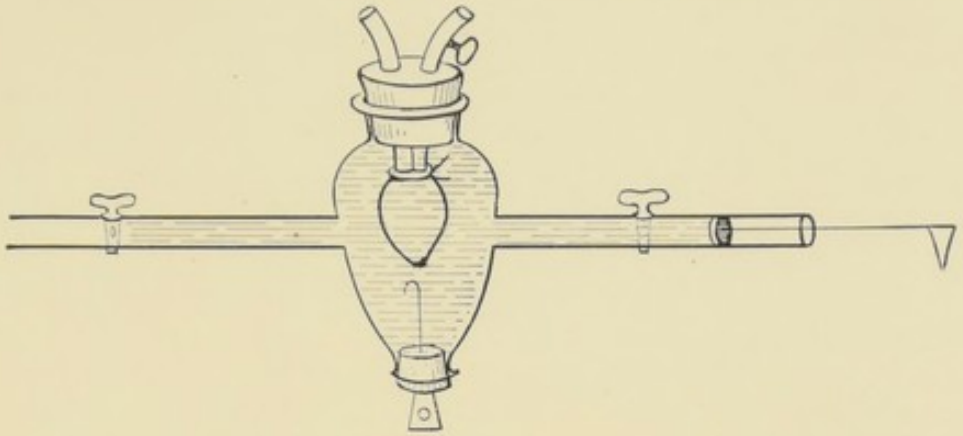


FIG. 13.—Diagram of Schäfer's cardiac plethysmograph. The heart is tied to a double cannula, through which the fluid containing the drug can pass to and from the cavity of the ventricle. The heart is then inserted into the air-tight bulb of the apparatus which contains oil. The alterations in the volume of the ventricle are communicated to the piston and thus a tracing is obtained.

involve much less injury to the heart, and allow the influence of the vagus and sympathetic nerves to be readily studied.[1]

PHYSIOLOGICAL ACTION OF DRUGS

Drugs must be in solution if they are to be readily absorbed and carried by the blood to the various tissues of the body. Water is the best solvent, and its effects upon the body must be studied before conclusions can be drawn concerning the action of any substances dissolved in it.

In the following experiments upon the action of various drugs it is important to remember that the doses necessary to produce characteristic effects upon isolated but still living muscle and nerve are often much larger than those sufficient to produce symptoms or even death of the animal. Further, it is obvious that in some cases a drug produces in the more highly-developed mammal effects different from those observed in the frog. This does not, however, invalidate such a method of

[1] The solution of the drug can be passed through a frog's heart by means of a cannula inserted into the hepatic veins. The contraction is recorded with the simple cardiograph (Brodie and Dixon).

study, for on the whole the effects are similar, and even the differences often throw light upon the mode of action of the drug.

Distilled Water

Distilled Water, H_2O, should be free from ammonia and traces of copper or other metals, which may be dissolved when the water is condensed in a metal worm and collected in metal receivers. It is important to study the action of water upon living tissues, for it is frequently used as a solvent of drugs.

Experiment IX.—*The Effect upon the Heart.*—A record of the contraction of the heart is taken, and then by means of a small pipette distilled water is passed in a gentle stream over the heart. If the heart contains a large quantity of blood it may be necessary to allow it to escape by a small incision in one of the auricles; otherwise the salts contained in the blood will pass into the distilled water and make it a saline solution, and the effect of pure water will not be readily observed. After the heart has been thoroughly treated with distilled water, its contractions become less frequent, but more prolonged (Fig. 14, Curve II.; Fig. 16, Curve II.; and Fig. 17, Curve I.). A further application will reduce the frequency and force of the contraction until the heart ceases to beat (Fig. 14, Curve III.; and Fig. 17, Curve III.).

The heart, however, is not dead, and if it be treated with normal saline solution, or, better, with normal tap-water saline solution, the contractions may be restored (Fig. 16, Curves II. and III.; and Fig. 17, Curves III. and IV.).

Another method of observing the effect of distilled water is to cut out the heart, and, after washing away the blood, to place it in a watch-glass filled with pure water. As a control, another heart is treated in a similar way, except that normal tap-water saline solution is used instead of water. The heart exposed to the action of the distilled water ceases to beat at a time when the control-preparation is contracting vigorously.

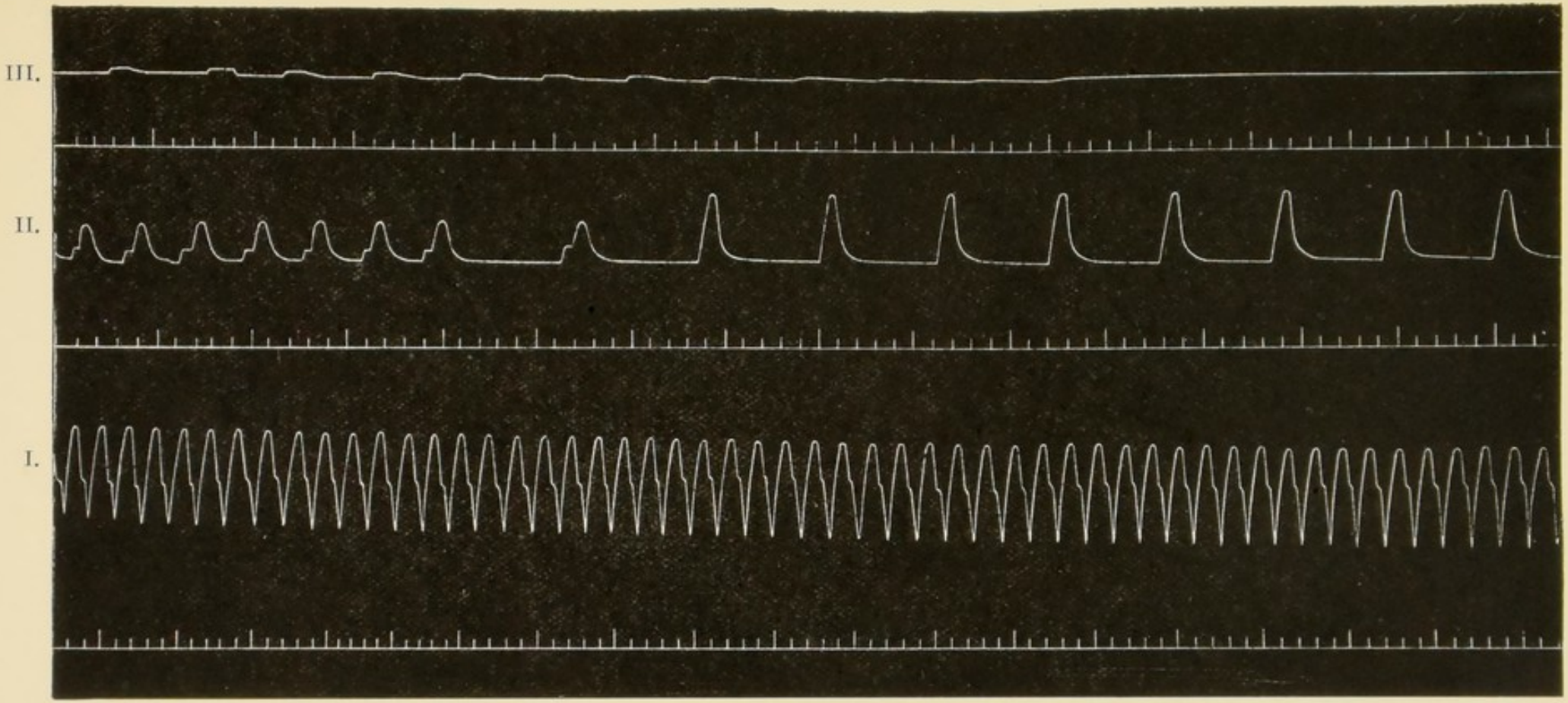


FIG. 14.—Contraction of the frog's heart. I. Normal. Temperature of air = 14°. II. Effect of distilled water free from ammonia. Temperature = 13·5°. III. Later effect of distilled water. The time is marked in seconds.

Experiment X.—*The Effect upon Muscle and Nerve.*—The gastrocnemius muscle and the sciatic nerve are dissected on each side of a pithed frog; each preparation is placed in a watch-glass and the minimal stimulus (see Expt. III. p. 3) is determined for both muscles and nerves. The excitability of the two preparations will be practically the same. One preparation, A, is now placed in a vessel of distilled water; the other, B, is covered with a wet watch-glass in order to prevent drying of the tissues. About five minutes later the excitability of the nerve and muscle in both preparations is again determined; the one, B, shows little or no change, but in the case of A there is a decrease in the excitability of both muscle and nerve. The preparation A is replaced in a fresh quantity of distilled water for about forty-five minutes; at the end of this time the nerve and muscle will have lost their excitability and will show obvious changes; the nerve will be whiter, more opaque and stiffer as compared with the control-specimen B; the muscle A will show a similar change, due to the action of the distilled water upon the globulins of the muscle. The excitability of the muscle and nerve in the preparation B will be retained for a long time, if precautions be taken to prevent evaporation. This is necessary, because living tissues contain a large percentage, at least three-quarters of their weight, of water.

This experiment shows that distilled water is a poison to muscle and nerve. It does not contradict the fact that distilled water can be swallowed without any obviously bad effects, for in the alimentary canal the water becomes a weak saline solution; salts are dissolved from the tissues or the contents of the digestive tract. The practical importance of the different physiological effects of distilled water and of weak saline solution is seen in the transfusion of saline solutions after severe hæmorrhage; distilled water rapidly breaks up the blood-corpuscles, but weak saline solutions do not. A nasal douche with weak saline solution causes less discomfort than one with distilled water.

Normal Physiological Saline Solution

Normal physiological saline solution is made by the addition of 0·6 to 0·7 per cent. of sodium chloride, NaCl, to pure distilled water. This fluid possesses the same osmotic pressure as the liquid of living tissues, and is called an "isotonic" solution. By its use the transference of water or salt from the tissue to the fluid is partly prevented, and the normal environment of the living cells is much less disturbed than it would be by distilled water.

Experiment XI.—*The Effect upon Red Blood-Corpuscles.*—The action of "isotonic," "hypoisotonic," and "hyperisotonic" solutions can be studied upon red blood-corpuscles. A drop

Fig. 15.—Diagrams to show the effect upon human red blood-corpuscles of I. isotonic, II. hypoisotonic, and III. hyperisotonic solution.

or two of normal physiological saline solution is added to a drop of human blood[1] just drawn from the finger, and the shape of the corpuscles is observed under a microscope; the corpuscles are not deformed, for the solution is isotonic. Distilled water is added to another drop of blood and is soon found to produce swelling and destruction of the corpuscles with the liberation of hæmoglobin; the water is hypoisotonic and passes into the corpuscle. If a third drop of blood be treated with strong salt solution, the corpuscles become crenated owing to the loss of water to the hyperisotonic solution.

[1] For human blood an isotonic solution should contain 0·9 per cent. of sodium chloride.

Experiment XII.—*The Effect upon the Heart.*—Although the application of normal saline solution will often restore an irregularly beating heart, and the rhythmic power to a heart, which has been treated with distilled water, yet it soon causes a more feeble and slower contraction. The continued application of the solution results in the cessation of all contraction, and the heart stops in diastole.

If by means of distilled water the heart's contraction be greatly diminished in frequency and rendered irregular (Fig. 16, Curve II.), normal saline solution will restore the beat (Fig. 16, Curve III.), but not to such a marked degree as tap-water saline solution (Fig. 17, Curves II. and IV.).

It sometimes happens that the heart beats irregularly but with a definite rhythm before the application of any fluid. In such cases normal saline solution generally restores and maintains for a considerable time a regular beat (Fig. 16, Curve I.).

The action of normal saline solution in these cases should be compared with that of a saline solution of similar strength but made with tap-water (Expt. XIV.).

Experiment XIII.—*The Effect upon Muscle and Nerve.*—Two muscle and nerve preparations are made from a pithed frog; they are placed in watch-glasses, and the minimal stimuli for the nerves and muscles are determined. The one preparation, A, is covered with distilled water, the other, B, with normal saline solution. A marked decrease in the excitability of both nerve and muscle of A will soon be observed (see Expt. X.), but in the case of B the excitability will be retained for hours and only gradually diminishes.

This experiment shows conclusively the value of the addition of a small quantity of salt in removing the poisonous effects of distilled water.

Normal Tap-water Saline Solution

The researches of Ringer have shown that the best saline medium for maintaining the contraction of the frog's heart is a

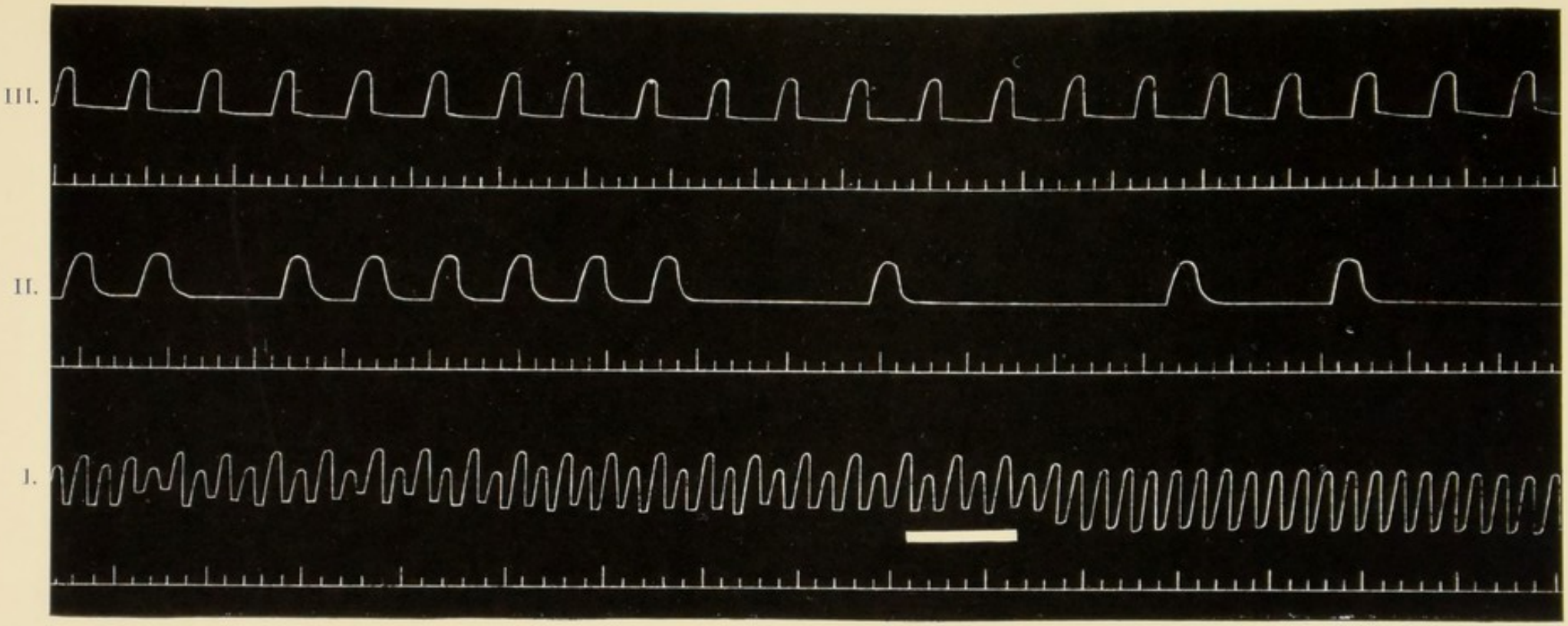


FIG. 16.—Contraction of the heart of a frog. I. Irregular beat ; no fluid had been placed on the heart. Normal saline (distilled water free from ammonia + 0·6 per cent. pure sodium chloride) applied at the point marked. The contraction becomes regular. II. Continuation. Effect of distilled water free from ammonia. III. Continuation. Effect of normal saline solution in restoring the contraction. The time is marked in seconds.

solution containing small quantities of calcium salts. Thus a ·6 per cent. solution of sodium chloride made with the New River tap-water has much greater sustaining properties in the case of the frog's heart than a solution containing a similar amount of sodium chloride but made with distilled water. Living tissues are, as Nägeli, Locke, and others have shown, extremely sensitive to traces of compounds of various heavy metals, such as copper, and are easily poisoned and killed thereby. It is important, therefore, to take tap-water after the water has been allowed to "run" for some time, and thus remove the water which has been stagnant in the service-pipes and has there dissolved small quantities of metal.

Experiment XIV.—*The Effect upon the Heart.*—A record of the contraction of the heart is taken before and after the blood has been allowed to escape.[1] This portion of the tracing will serve as a control. The record is continued, and from a pipette a gentle stream of normal tap-water saline solution is allowed to flow over the heart. A regular beat may be maintained for hours, if the heart be moistened from time to time with the solution.

Distilled water is then applied until the heart-beat is greatly diminished in force (Fig. 17, Curve I.); at this stage normal tap-water saline solution is supplied and the heart soon regains its former power of contraction (Curve II.). For a second time distilled water is allowed to flow over the heart until its contractions cease (Curve III.). The heart, however, can be again restored by the application of normal tap-water saline solution, and will continue to beat for hours with considerable force and regularity (Curve IV.).

This experiment shows conclusively that (i.) normal tap-water saline solution is a good medium for the heart; (ii.) distilled water is poisonous and reduces the force of the heart-beat until it ceases; and (iii.) the contraction of the heart can

[1] See p. 14.

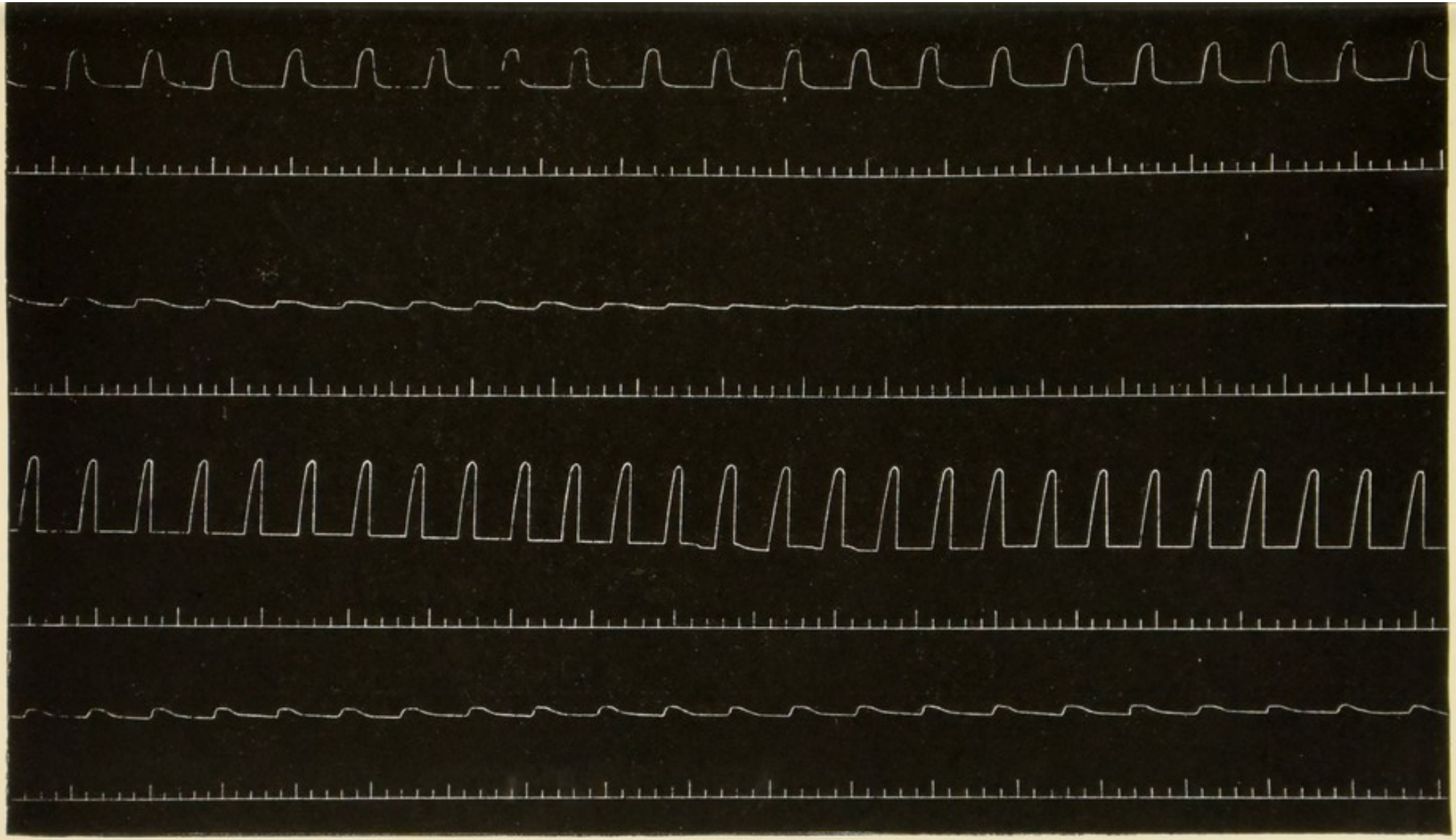


FIG. 17.—Contraction of the heart of a frog. I. Effect of distilled water. Temperature = 16·25°. II. Contraction restored by normal tap-water saline solution. Temperature = 16·5°. III. Effect of distilled water again applied to the heart. IV. Contraction restored a second time by normal tap-water saline solution. The time is marked in seconds.

be restored and maintained for a long time by normal tap-water saline solution.

In practical medicine and surgery normal tap-water saline solution, which has been previously sterilised by boiling, is the most suitable fluid for transfusion, washing out the peritoneal cavity, and in some cases cleansing the cavities of wounds.

Alcohol

Ethyl alcohol (alcohol ethylicum), C_2H_5OH, is a colourless volatile liquid prepared by the fermentation of malt sugar with yeast (saccharomyces cerevisiæ). The equation $C_6H_{12}O_6 = 2C_2H_5OH + 2CO_2$ approximately expresses the process. It has a characteristic odour and taste, a specific gravity about 0·794, boils at 78·3° (173° F.), and has been converted into a solid at a temperature of −130·5°. It mixes in all proportions with water.

Experiment XV.—*The Effects of Poisonous Doses.*—The cerebral hemispheres of a frog are destroyed, and after the slight shock of this operation has passed off, 15 minims (0·888 c.c.) of a mixture, containing 1 part of absolute alcohol to 2 parts of tap-water saline solution, are injected under the skin of the back. The immediate effect is a short stage of excitement. Within five minutes a delay is observed in the recovery of the hind legs after a jump, and, if placed upon its back, the frog does not readily turn over. Reflex movements soon become more and more sluggish, and the frog lies in a toneless and almost completely paralysed condition. Under the skin the slow and forcible beating of the heart can generally be seen, and from time to time the respiratory movements of the floor of the mouth.

After about half-an-hour recovery begins; the muscles slowly regain their tone, and the frog assumes a more natural attitude and crawls about in a sluggish manner. If the frog be kept moist under a bell-jar, complete recovery from the action of the drug occurs after several hours.

Alcohol produces paralysis by its action upon the central nervous system, for if, during the paralysis, the sciatic nerve and the gastrocnemius muscle respectively be stimulated with a weak induction-current, a ready response is obtained.

A fatal dose for a frog is one containing about 10 minims (0·592 c.c.) of absolute alcohol; the quantity of water used to dilute the drug will obviously affect the rate of absorption and excretion. It will be observed in the next experiment that strong doses paralyse the heart and thus stop the circulation of the blood. Examination of the body after death shows the ventricle to be firmly contracted but the auricles distended with very venous blood.

Experiment XVI.—*The Effect upon the Heart.*—A tracing of the heart-beat of a pithed frog is taken in the ordinary way; two or three drops of tap-water saline solution are placed on the heart and the effect recorded. Now two drops of a mixture of 1 part of absolute alcohol to 2 parts of tap-water saline solution are placed upon the heart. There is an immediate effect; the heart loses tone and contracts more slowly and feebly. This is quickly followed by contractions of progressively increasing energy and slower relaxation, so that there is produced a "staircase" effect (Fig. 18, Curve I.), and the cardiac muscle soon recovers its tone (Fig. 19). After a minute or two the heart may cease to beat in the diastolic phase, but will respond to a single electrical stimulus with a series of forcible beats and then cease to beat for another period (Fig. 18, Curve II.). A further electrical stimulus will start another series of beats, and then the heart may beat regularly with greatly increased force and so continue for many minutes (Fig. 18, Curve III.).

Alcohol, when it is applied in this manner, diminishes the frequency but greatly increases the force of the cardiac contraction. In strong doses the effect is to remove the automatic power of rhythmic contraction, but not to paralyse the muscle, for electrical stimulation will bring about a series

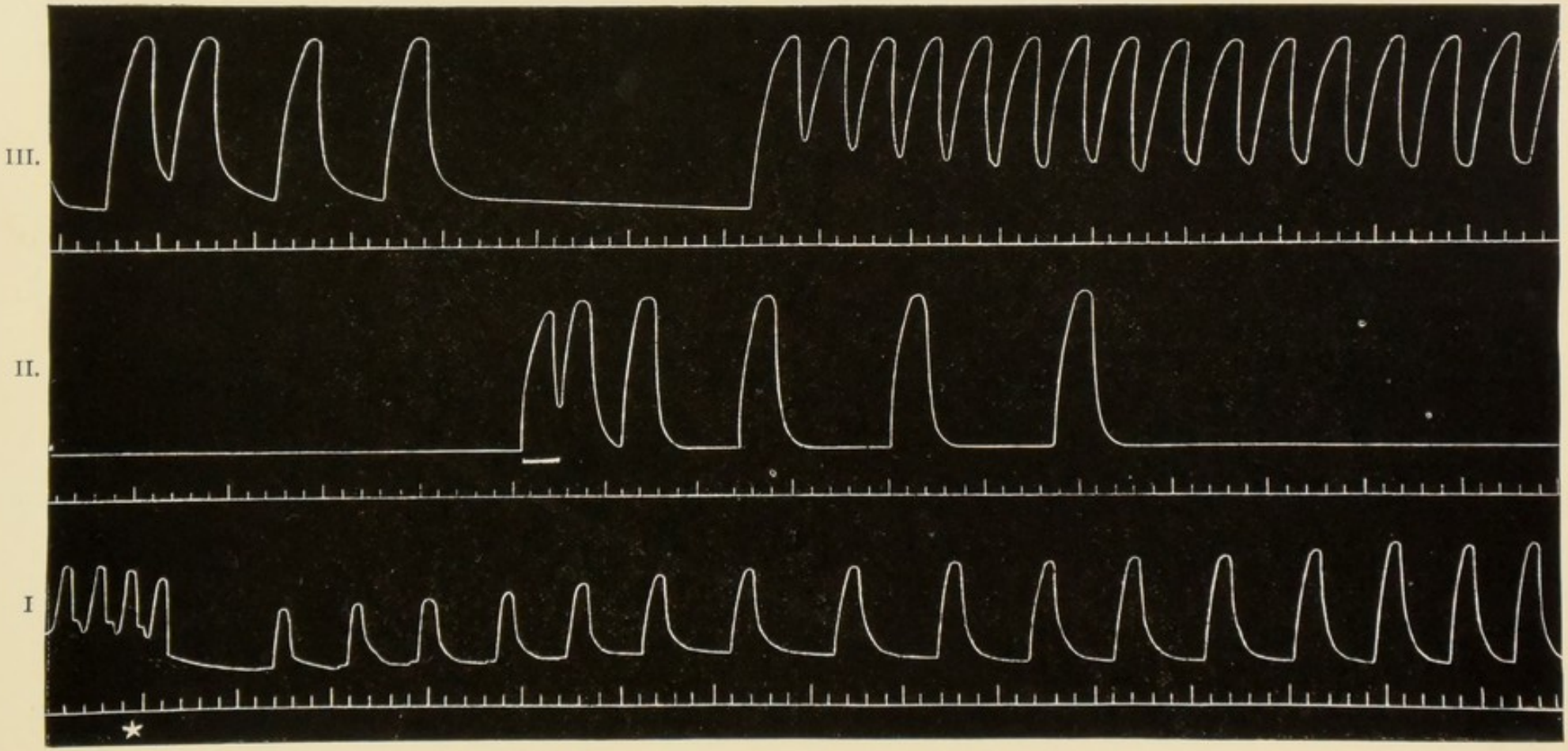


FIG. 18.—Contraction of the heart of a frog. Effect of alcohol. Temperature of air, 13°. I. Begin with normal tap-water saline. At point * a drop or two of a mixture containing 1 part of absolute alcohol to 2 parts of tap-water saline was placed on heart. II. Later effect. Heart had ceased to beat for two minutes before this curve was taken. Electrical stimulation of the heart at point marked. III. Later effect. After short electrical stimulation the heart commenced to beat with increased tone and so continued for some time. The time is marked in seconds.

of vigorous but slow contractions. Still stronger doses kill the heart.

It is necessary to remember that the effect of the drug depends upon the dose and its penetration into the muscle.[1] The alcohol evaporates, and thus the dose is gradually diminished.

Experiment XVII.—*The Effect upon the Nervous System.*—The results of the first experiment show that alcohol first excites and then paralyses the central nervous system; for a time reflex action is abolished, but recovery may occur, if the dose be not too large.

Experiment XVIII.—*The Effect upon Muscle and Nerve.* — Large doses of alcohol applied directly to muscle and nerve at first diminish and then destroy the excitability of both tissues. This can be observed by the dissection of the gastrocnemius muscle and the sciatic nerve in its entire length on each side of a pithed frog, placing the muscle of preparation A in

[1] See note p. 30.

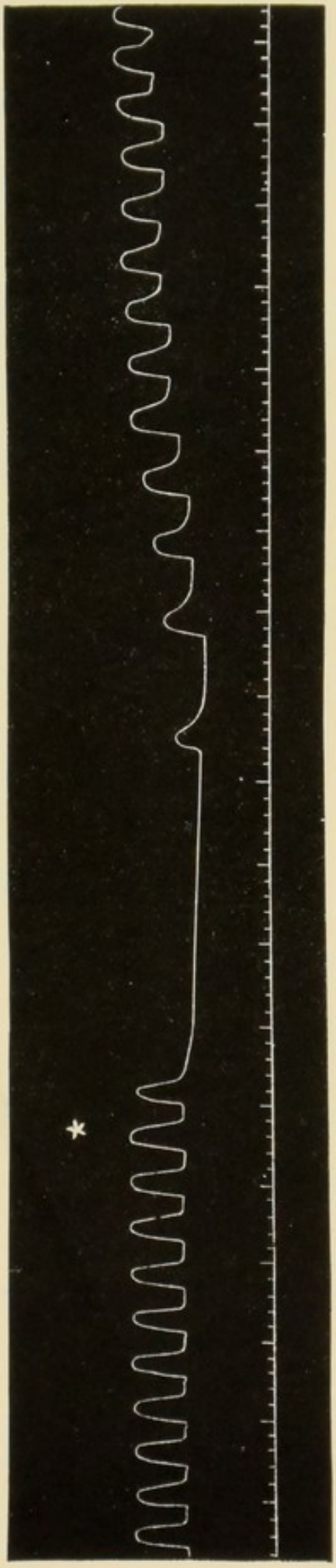


Fig. 19.—Heart of frog. The effect of a previous dose of alcohol (1 part absolute to 2 parts tap-water saline) had almost passed off when at point marked * a further dose (1 in 3) was placed on the heart used for the record (Fig. 18). The heart at first ceases to beat and loses tone, there is then a recovery of the rhythmic power of contraction and of the tone of the muscle. The time is marked in seconds.

a watch-glass containing 1 part of absolute alcohol to 2 parts of tap-water saline solution, but leaving the nerve outside; the nerve of preparation B is placed in another watch-glass containing alcohol of the same strength, while the muscle is in this case left outside. In about ten minutes the excitability of the tissues is so diminished that a very slight response is seen when the nerves are stimulated with a strong induction current. A few minutes later the muscle A and the nerve B no longer respond to stimulation with the strongest current.

Ether

Ether, $(C_2H_5)_2O$, is a colourless, very volatile and inflammable liquid with a specific gravity about 0·740. It has a characteristic odour and a pungent taste; its boiling-point is 34·9° (95° F.). It is not very soluble in water, 1 part in 9 parts of water.

Ether is prepared by the distillation of alcohol with sulphuric acid; the chemical change is represented by the following equations:—

$$\left.\begin{matrix}H\\H\end{matrix}\right\}SO_4+\left.\begin{matrix}C_2H_5\\H\end{matrix}\right\}O=\left.\begin{matrix}C_2H_5\\H\end{matrix}\right\}SO_4+\left.\begin{matrix}H\\H\end{matrix}\right\}O$$

$$\left.\begin{matrix}C_2H_5\\H\end{matrix}\right\}SO_4+\left.\begin{matrix}C_2H_5\\H\end{matrix}\right\}O=\left.\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\right\}O+\left.\begin{matrix}H\\H\end{matrix}\right\}SO_4.$$

Experiment XIX. — *The Effects of Poisonous Doses.*— Under the skin of the back of a frog, whose cerebral hemispheres have been destroyed, are injected 7 minims (·414 c.c.) of ether. The immediate effect is great excitement, which soon subsides; the frog becomes quieter but shows incoordination in its movements. The hind legs become more and more helpless, and about fifteen minutes after the administration of the drug the frog is profoundly anæsthetised and lies in a toneless paralysed condition. Respiratory and reflex movements cease, and, apart, it may be, from the slow and

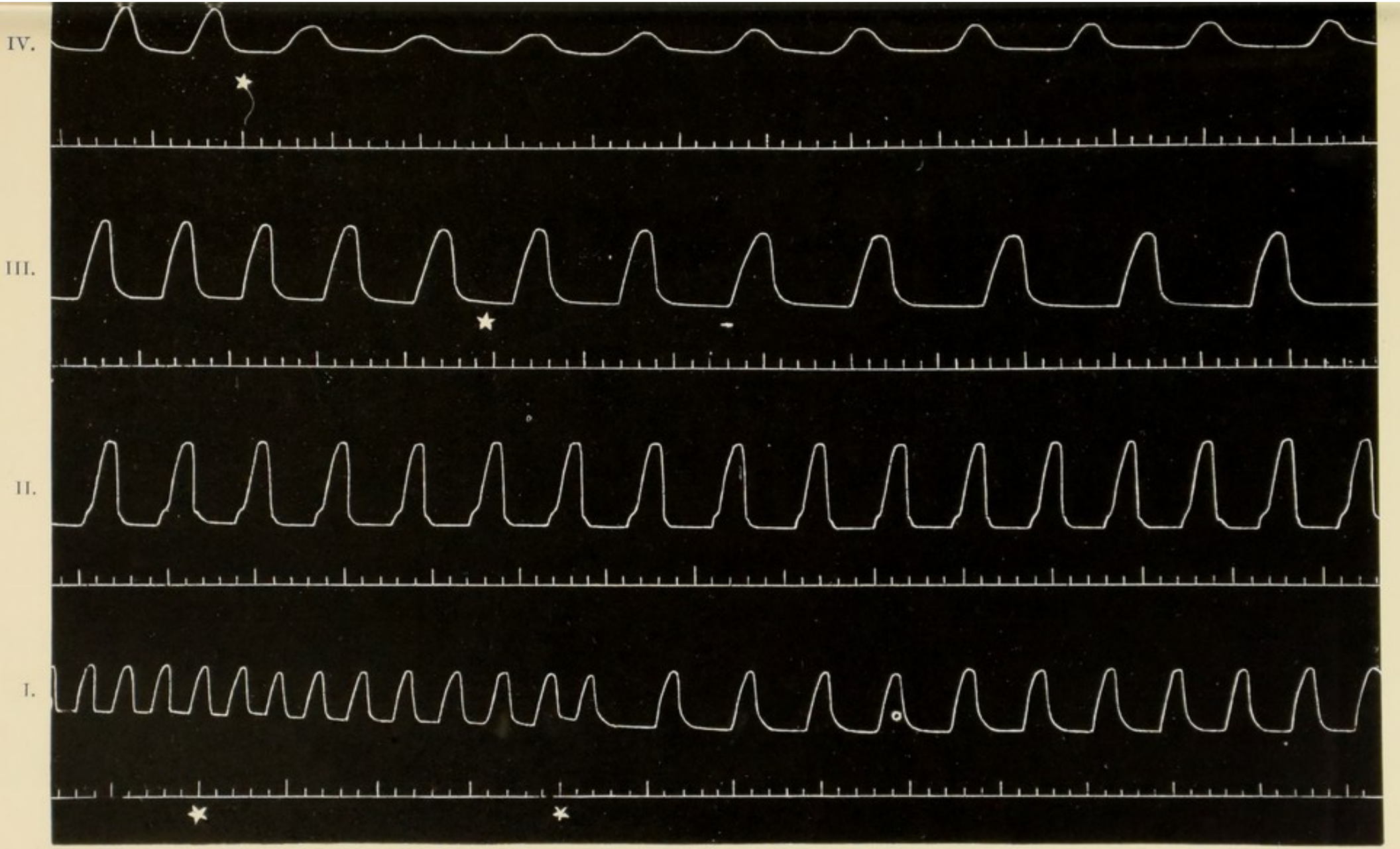


FIG. 20.—Contraction of the heart of a frog. Effect of ether. I. Begins with normal, then drops of ether-water were applied at the points indicated by the stars. II. Later effect of a further dose. III. Effect of a drop of pure ether applied to the same heart at the point indicated by the star. IV. Further effect of two drops of pure ether applied at the point indicated by the star. The time is marked in seconds.

Fig. 21.—Contraction of the heart of a frog. Effect of ether. This curve is a continuation, two minutes later, of Curve I., Fig. 20, but it has been reduced to one-half the actual size. At the point indicated by the star a drop of ether-water was applied. The time is marked in seconds.

forcible beating of the heart, the frog appears to be dead. If, however, the frog be kept moist for several hours in a shallow plate, filled with water and covered by a bell-jar, complete recovery from the effects of the drug may occur.

The anæsthesia and paralysis are due to the action of the drug upon the central nervous system, for if during the stage of paralysis the sciatic nerve and the gastrocnemius muscle are exposed and stimulated with a weak induction shock, there is a ready response, showing that these tissues are still excitable.

A fatal dose for a frog is 8 to 10 minims (0·473 to 0·592 c.c.). After death from an overdose of this drug the ventricle of the heart is found to be firmly contracted, but the auricles greatly distended with very venous blood.

Experiment XX.—*The Effect upon the Heart.*[1]—A tracing of the heart-beat of a pithed frog is taken for a minute or two in order to obtain a normal curve; then two drops of tap-water saline solution saturated with ether are placed upon the heart. The effect is some loss of tone and diminished frequency, but increased force in the contraction of the ventricle (Fig. 20, Curve I.). After a record has been taken for about two minutes a further dose is applied; the heart may then cease to beat and may remain in the diastolic phase for about

[1] See note p. 30.

half a minute. Isolated beats now follow, and then the heart beats regularly with increased force (Fig. 21, which has been reduced to one-half the size of the actual tracing). The further effect is well shown in Figure 20, Curve II.; the rate of contraction is four in fifteen seconds, as compared with seven before the application of the drug, but the height of the contraction is almost doubled. A drop of pure ether will reduce the rate of contraction still further, and will retard the relaxation of the ventricle (Fig. 20, Curve III.). A still stronger dose greatly diminishes the force of the contraction; the ventricle contracts and relaxes slowly (Fig. 20, Curve IV.).

Experiment XXI.—*The Effect upon Muscle and Nerve.*—Two muscle and nerve preparations are made, and the minimal stimulus for each nerve and muscle is determined. The muscle of one preparation (A) is then placed in a watch-glass filled with normal tap-water saline saturated with ether, but its nerve is left outside; the nerve of the second preparation (B) is placed in the liquid, but its muscle is kept outside. The excitability of the nerve B rapidly decreases, and in a few minutes is entirely lost; the muscle B contracts readily to direct stimulation. In the case of the muscle A there is a gradual loss of excitability to direct and indirect stimulation; the muscle becomes whiter and somewhat contracted, and soon shows a marked decrease in its excitability.

In pure ether the muscle rapidly passes into a shortened and rigid condition. These experiments show that ether is a poison to both muscle and nerve. Similar effects are produced by the vapour of ether.

Chloroform

Chloroform, $CHCl_3$, is a colourless heavy liquid with a pleasant odour and a sweet taste. It has a specific gravity, 1·490; it is volatile and is soluble in water in the proportion of 1 to 200. Its boiling-point is 62° (143° F.).

It is prepared by the distillation of alcohol with chlorinated lime and slaked lime. The reaction may be represented by the following equation :—

$$4C_2H_6O + 8CaCl_2O_2 =$$
Alcohol Calcium hypochlorite
$$2CHCl_3 + 3Ca(CO{\cdot}OH)_2 + 5CaCl_2 + 8H_2O$$
Chloroform Calcium formate Calcium chloride Water.

Experiment XXII.—*The Effects of Poisonous Doses.*—Under the skin of the back of a frog, whose cerebral hemispheres have been destroyed, is injected a dose of 5 minims (0·296 c.c.) of chloroform. At first there is a stage of great excitement, which is quickly followed by a period of rest. In about six minutes the frog shows marked inco-ordination and its hind legs are partly paralysed. A few minutes later there will be marked anæsthesia, paralysis, and total absence of reflexes. If, however, the frog be kept moist in a shallow plate full of water and covered by a bell-jar it may, after seven or eight hours, completely recover from the effects of the drug.

Chloroform affects the central nervous system, for it can be shown by stimulation of the sciatic nerve and the gastrocnemius muscle that these tissues are excitable even when the general anæsthesia and paralysis are most profound.

A fatal dose for a full-sized frog is 8 minims (0·472 c.c.). An examination of the heart after death shows that the ventricle is empty and contracted, but the auricles are greatly dilated and distended with very venous blood.

Experiment XXIII.—*The Effect upon the Heart.*[1]—A record of the contraction of the heart is taken both before and after it has been moistened with normal tap-water saline solution. These curves will serve as a control. Two or three drops of normal tap-water saline solution saturated with pure chloro-

[1] Brodie and Dixon have recently found that in the case of chloroform, ether, and alcohol a different effect is observed if the drug is perfused through the heart.

form (about 1 in 200) are now placed upon the heart; the first effect is generally a loss of tone; the heart dilates slightly, and the base line falls a little; the beat is smaller and slower. In a few minutes the contraction improves, and in some cases may become more forcible and of longer duration than it was before the application of the drug.

If a larger dose of the solution or one drop of pure chloroform be applied, the heart gives one or two feeble beats and

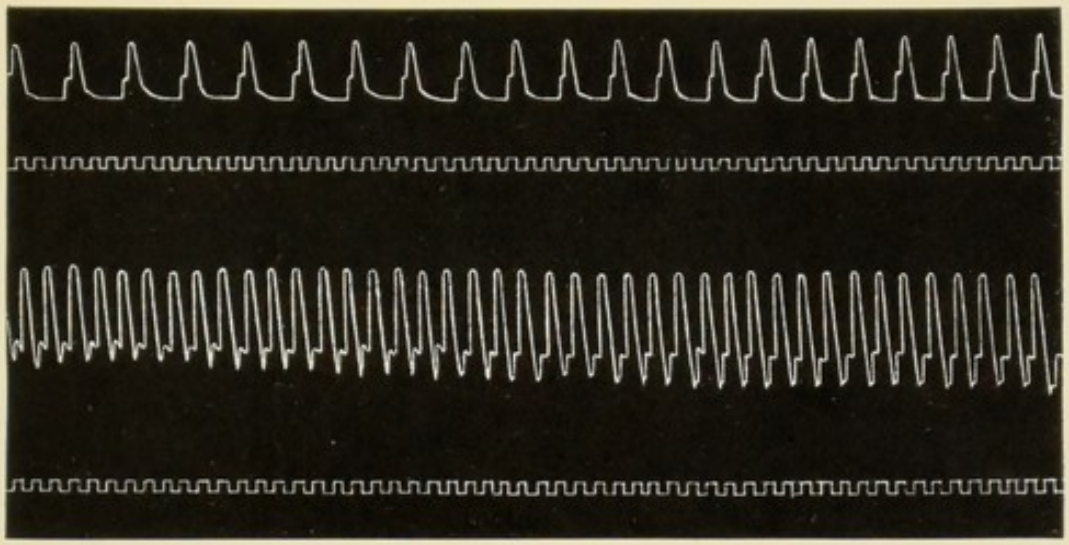


FIG. 22.—Contraction of the heart of a frog. I. The heart had been moistened only with normal tap-water saline solution. II. The effect of a previous application of several drops of normal tap-water saline solution saturated with chloroform (1 in 200). The time is marked in seconds.

then ceases to contract for one or two minutes (Fig. 24, Curves I. and II.). It then begins to beat with increased vigour; the height and duration of the contraction are greater, but the frequency is not so great as in the normal heart. The strength of the dose has been diminished by the evaporation of the chloroform. The standstill of the heart in diastole is generally followed by big but slow contractions; this effect is probably due to the storage of energy, of combustible material, in the heart during the abnormally long period of rest.

The prolonged action of the solution of chloroform causes marked dilatation of the auricles; they may be distended with fluid but contract so feebly that they cannot force it into the ventricle. At this stage the ventricle may be contracting well.

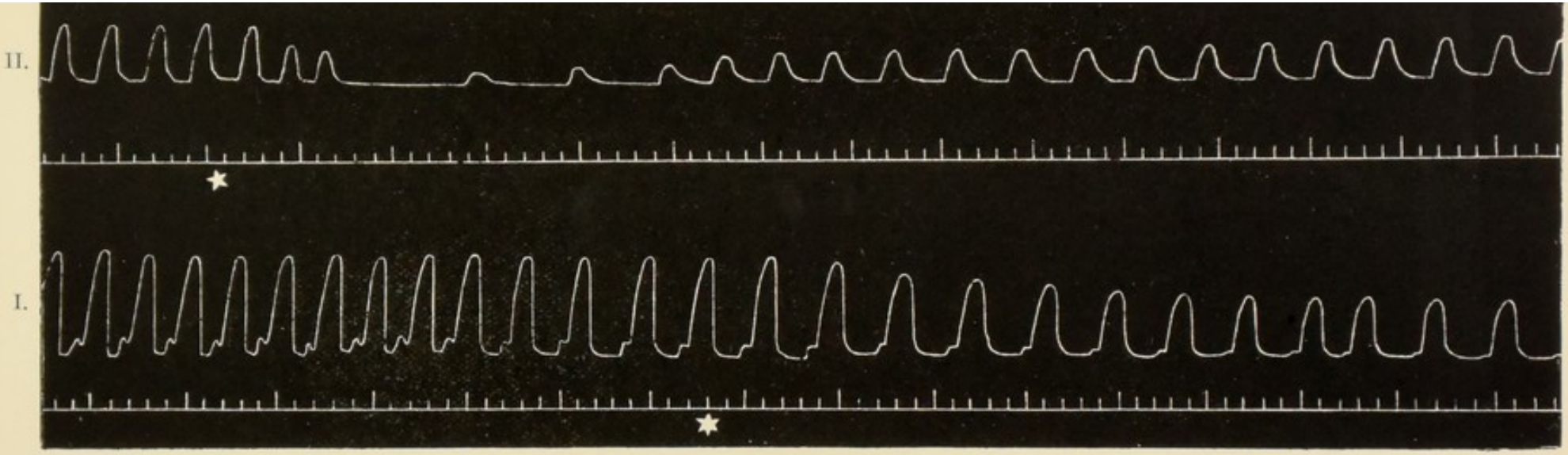


FIG. 23.—Contraction of the frog's heart. The effect of chloroform. I. The heart had been previously treated with chloroform, but the direct effect had passed off. At the point indicated by the star a drop of pure chloroform was allowed to flow over the heart. The contractions became smaller and slower. II. Another heart, which had been previously treated with chloroform-water (1 in 200). At the point indicated a further dose was applied. The time is marked in seconds.

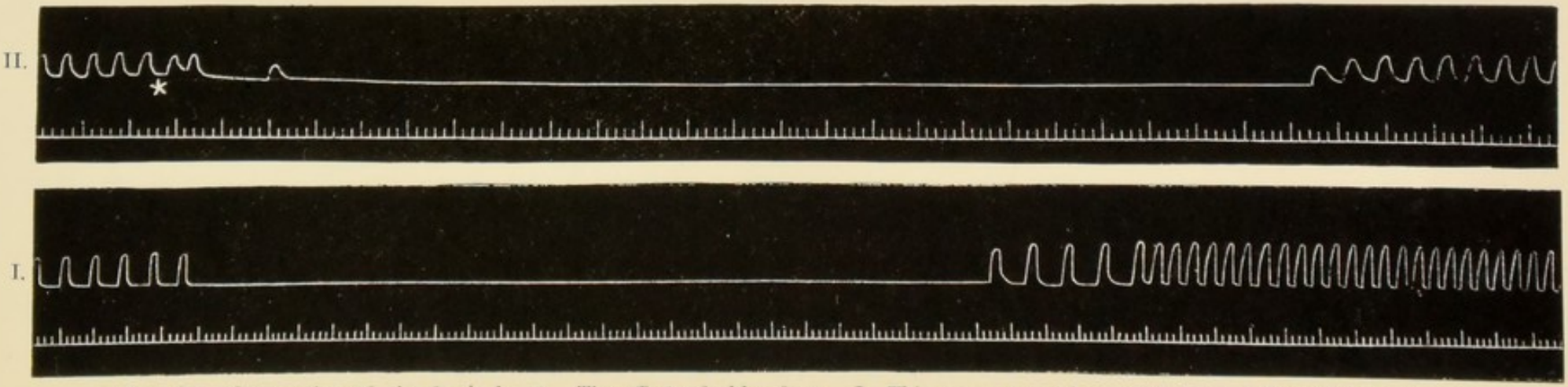


FIG. 24.—Contraction of the frog's heart. The effect of chloroform. I. This curve was taken two minutes after the application of three drops of pure chloroform to a heart which had previously been treated with chloroform-water. The tracing has been reduced to one-third its actual size. II. The heart had been previously treated with chloroform-water; at the point indicated by the star one drop of pure chloroform was applied. The tracing has been reduced to one-half its actual size. The time is marked in seconds.

Experiment XXIV.—*The Effect upon the Nervous System.*—The first experiment upon the action of chloroform showed that it affected the central nervous system, and produced inco-ordination, then deep anæsthesia and paralysis. If the dose be not too large, the effects gradually pass off and complete recovery from the action of the drug occurs.

Experiment XXV.—*The Effect upon Muscle and Nerve.*—Two muscle and nerve preparations are made, and the minimal stimuli for muscle and nerve are determined. The muscle of preparation A is placed in a watch-glass filled with normal tap-water saline solution saturated with chloroform; the nerve is kept outside; the nerve of preparation B, on the other hand, is placed in the fluid; the muscle remains outside. In a few minutes stimulation of the nerves A and B fails to produce a contraction, but the muscles respond to direct stimulation. There is, however, a rapid decrease in the excitability of the muscle A, and in a few minutes more it becomes shorter, rigid and opaque, and loses its excitability. The muscle B retains its excitability and contracts vigorously when it is directly stimulated. Chloroform is, therefore, in doses of 1 in 200, a rapid poison of muscle and nerve.[1]

Chloral Hydrate

Chloral hydrate, $CCl_3 \cdot CHO \cdot H_2O$, the hydrate of trichloraldehyde, is a white crystalline substance with a peculiar pungent odour, a caustic taste and a neutral reaction. It is readily soluble in water and melts at a temperature of 46° (115° F.).

Experiment XXVI.—*The Effects of Poisonous Doses.*—Under the skin of a brainless frog are injected 10 minims (0·592 c.c.) of a 2 per cent. solution of chloral hydrate in normal tap-water saline; at first there is some excitement, then inco-ordination of movements, sluggishness and a marked

[1] Similar effects are produced by the vapour of chloroform.

decrease in excitability. Recovery from the influence of the drug will occur in about twelve hours, if the frog be kept in a plate full of water and covered by a bell-jar.

A dose of 10 ♏ (0·592 c.c.) of a 4 per cent. solution will in about twenty minutes abolish all reflex action and the frog lies in an apparently lifeless condition. An examination of the web of the foot under the low power of a microscope shows that the heart-beat is feeble and the circulation is failing. The heart soon ceases to beat and death is the result. At the seat of injection there is some local irritation, and the skin becomes discoloured. The ventricle and auricles are found after death to be slightly distended with venous blood.

Experiment XXVII.—*The Effect upon the Heart.*—A record of the contraction of the heart is taken; a few

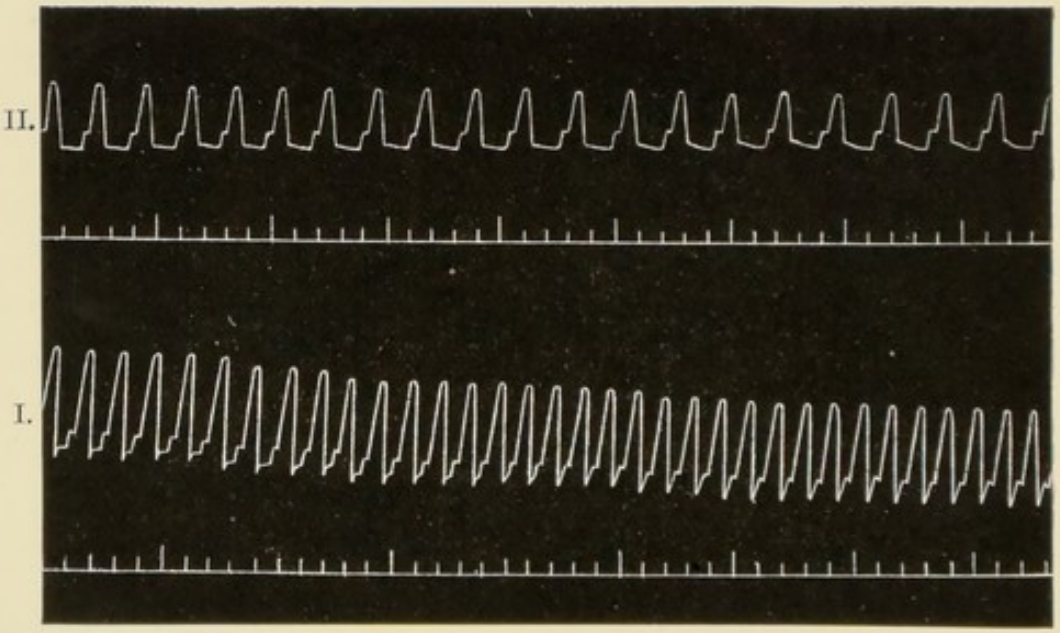


Fig. 25.—Contraction of the frog's heart. I. before and II. after the application of chloral hydrate, 1 part in 100 parts of normal tap-water saline solution. The drug causes a smaller and slower beat. The further action of the drug is shown in the first three contractions of the next tracing (Fig. 26). The time is marked in seconds.

drops of normal tap-water saline are applied and the record is continued. Stimulation of the vago-sympathetic

nerve will stop the beat and the inhibition will be followed by the characteristic after-effect (Fig. 8). A few drops of a 1 per cent. solution of chloral hydrate in normal tap-water saline are applied. The beats will soon become smaller and slower (Fig. 25, Curve II.). Stimulation of the vago-sympathetic nerve will still inhibit the heart, but the recovery is delayed and the after-effect is much less marked (Fig. 26). A further application of the drug causes considerable dilatation of the auricles, and later a smaller dilatation of the ventricle.

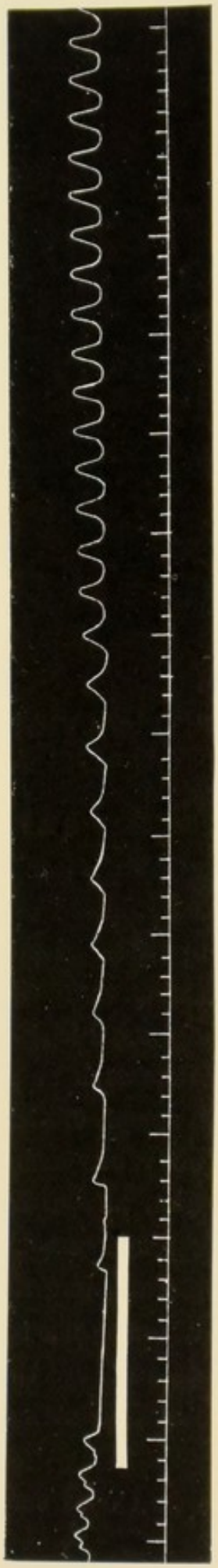


FIG. 26.—Contraction of the frog's heart. The effect of chloral hydrate, 1 part in 100 parts of normal tap-water saline solution. The vago-sympathetic nerve was stimulated with a strong faradising current during the period marked by the white line. The time is marked in seconds.

EXPERIMENT XXVIII.—*The Effect upon the Nervous System.*—The results of the first experiment upon the action of chloral hydrate show that it first increases the excitability of the central nervous system, then diminishes it and causes inco-ordination. A stronger dose abolishes all reflex action. The nerves and muscle, however, can be excited by stimuli applied to them.

EXPERIMENT XXIX.—*The Effect upon Muscle and Nerve.*—Two muscle and nerve preparations are made, and their excitability is tested in the ordinary manner. The nerve of preparation A and the muscle of preparation B are placed in a watch-

glass filled with a 1 per cent. solution of chloral hydrate in normal tap-water saline. An increase in the excitability of nerve A will be observed, but the muscle B will show a marked decrease in excitability, and in about twenty minutes fails to respond to the strongest direct stimulation. The muscle looks whiter, and is wrinkled; it has passed into rigor. The nerve A, even at the end of three-quarters of an hour, retains its increased excitability.

A stronger solution at first irritates and then paralyses nerve.

Strychnine

Strychnine, $C_{21}H_{22}N_2O_4$, is a very poisonous alkaloid obtained from the seeds of *Strychnos nux vomica*. It is a colourless crystalline substance sparingly soluble in water, 1 in 6700. The presence of acids makes the alkaloid more soluble in water owing to the formation of a salt.

Experiment XXX.—*The Effects of Poisonous Doses.*—Under the skin of a brainless frog are injected 10-15 ♏ of a saturated solution of strychnine in normal tap-water saline. In two or three minutes it will be observed that the frog cannot readily draw up its hind legs after a jump, and soon the reflex excitability of the spinal cord is so much increased that a slight touch or puff of wind upon the skin brings about a general spasm of the muscles. Convulsions quickly follow, and the body becomes rigid and rests on the mouth and toes in a position known as *emprosthotonus*. This attitude is due to the different strength of the various muscles; all are thrown into contraction, but the stronger overcome the weaker. The muscles are somewhat relaxed after the convulsions, but are again sent into tetanus by the slightest stimulus applied to the skin.

These *tonic* contractions are followed by prolonged twitches or *clonus*.

The spinal cord soon loses its excitability, and the frog lies

in this condition for several hours; if, however, it be kept in shallow water and covered by a bell-jar the excitability will return and recovery from the action of the drug occur in less than twelve hours. This is due to the excretion of the strychnine by the kidneys. The urine of a frog poisoned by strychnine will produce the characteristic convulsions when it is injected into another frog.

If, during the stage of convulsions, a probe be pushed down the vertebral canal, so as to destroy the spinal cord, the convulsions cease at once, showing that the drug acts upon the ganglion cells and their dendrites.

The death of a frog from a larger dose is quickly followed by well-marked *rigor mortis.*

Experiment XXXI.—*The Effect upon the Nervous System.*—The cerebral hemispheres of a frog are destroyed and then the gastrocnemius muscle is prepared. A strong ligature is placed under the gastrocnemius and tightly tied round the upper portion of the tibio-fibula and the remaining muscles; the leg is then removed below the ligature; this method of precaution prevents hæmorrhage. A pin is placed through the lower extremity of the femur and is pushed firmly into the cork of the myograph; a piece of moist flannel is then pinned down over the trunk to prevent the contractions of the muscles of the trunk from disturbing the lever connected with the gastrocnemius muscle.

A dose of strychnine similar to that used in the last experiment is injected under the skin of the back. Twitches and convulsions soon begin, and if a signal marking seconds be simultaneously recorded the twitches of the tetanus can be observed to number about eight in a second. This is a measure of the rate of discharge of impulses from the nerve-cells of the spinal cord. The stage of incomplete *tetanus* is followed by one of *clonus.* The following curves illustrate the tetanus (Fig. 27); the curve of clonus is similar to that produced by hydrastine (Fig. 34).

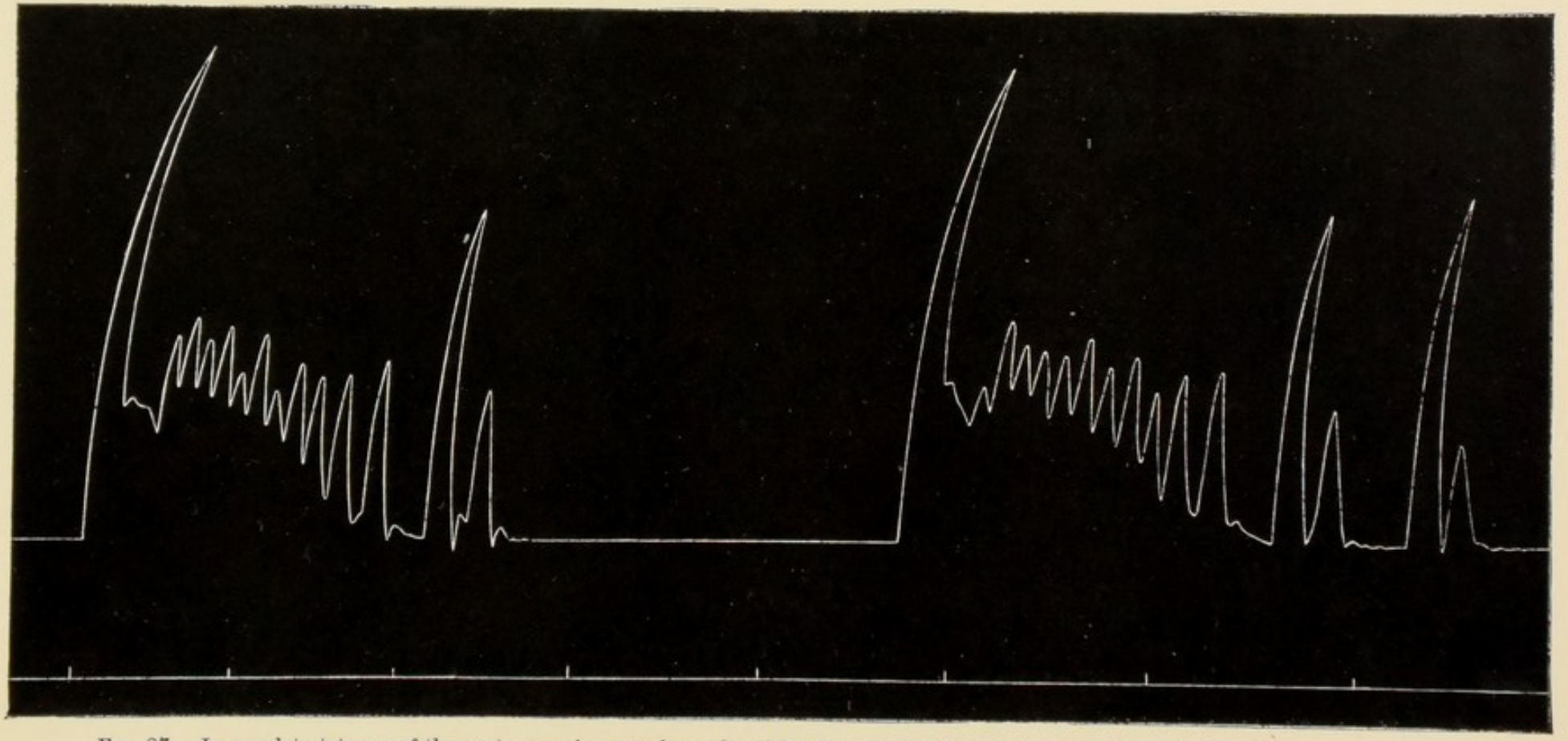


FIG. 27.—Incomplete tetanus of the gastrocnemius muscle produced by the action of strychnine upon the spinal cord of a brainless frog. The time is marked in seconds. Temperature of air = 23°.

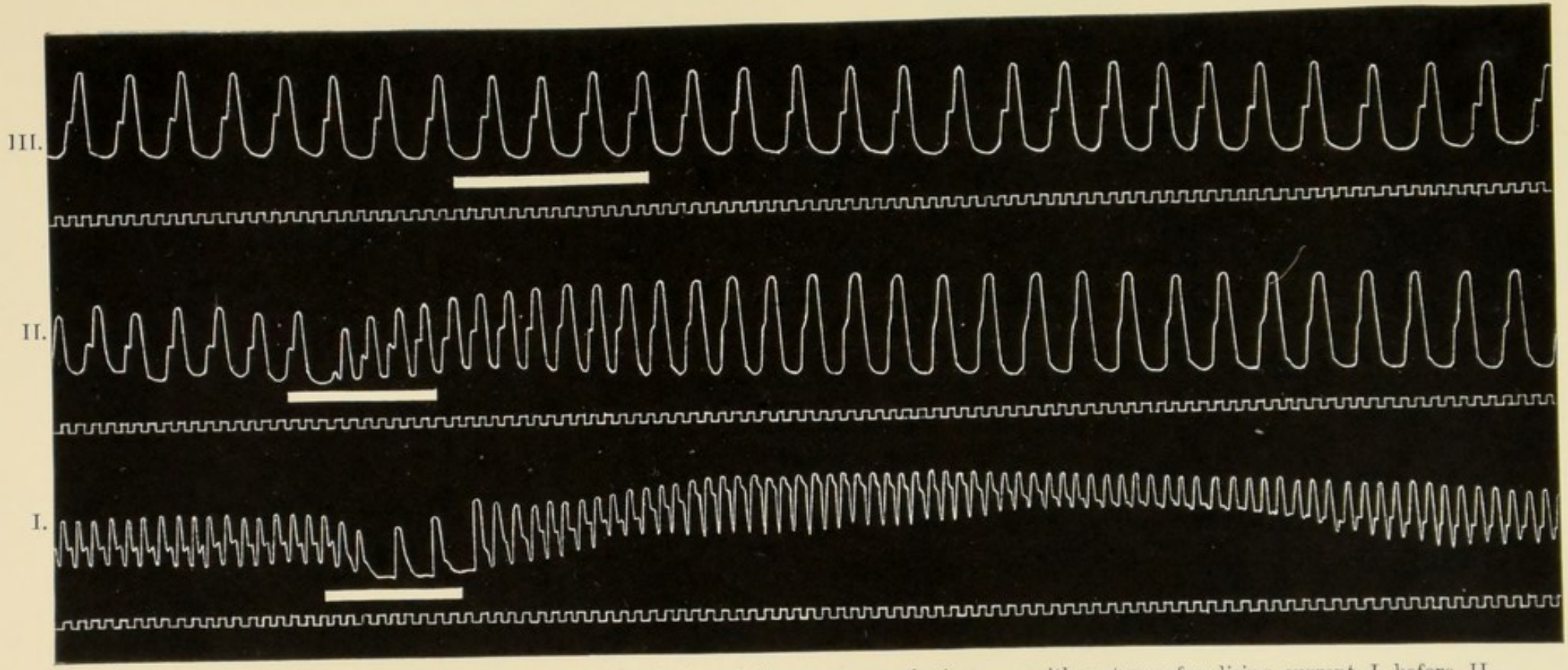


FIG. 28.—Contraction of the heart of a frog. Stimulation of the vago-sympathetic nerve with a strong faradising current, I. before, II. after the application of a few drops of a saturated solution of strychnine in normal tap-water saline solution, and III. after further doses of strychnine. The period of stimulation of the vago-sympathetic nerve is shown by the white line. The time is marked in seconds.

Experiment XXXII.—*The Effect upon the Heart.*—The vago-sympathetic nerve is exposed and a record is taken of the contraction of the heart. A few drops of normal tap-water saline solution are applied to the heart, the record is continued, and then the vago-sympathetic nerve is stimulated by a strong faradising current. The inhibitory action of the vagus and the after-effect are observed (Fig. 28, Curve I.). A few drops of a saturated solution of strychnine in normal

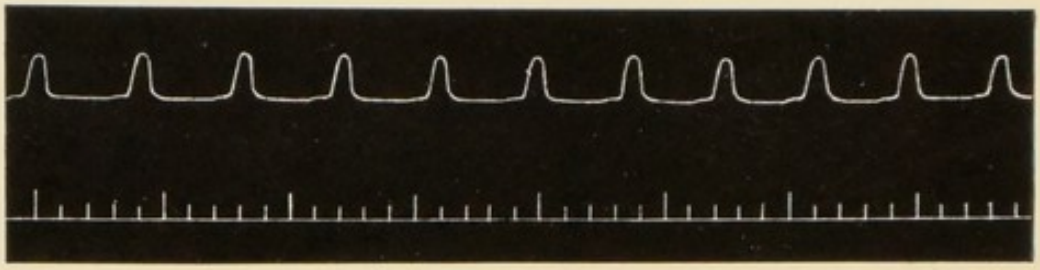


Fig. 29.—Contraction of the heart of a frog. The effect of prolonged action of a saturated solution of strychnine in normal tap-water saline solution (1 in 7000). The time is marked in seconds.

tap-water saline (1 in 6700) are allowed to flow over the heart. In a few seconds the heart-beat becomes slower but larger; the vago-sympathetic is again stimulated. Inhibition is not so marked; there is an after-effect, but the contractions are slow (Fig. 28, Curve II.). Further doses of strychnine are given and the stimulation is repeated. The inhibitory effect of the vagus is removed (Fig. 28, Curve III.).

The prolonged action of the drug is to produce a slow and feeble beat (Fig. 29).

Experiment XXXIII.—*The Effect upon Muscle and Nerve.*—Two muscle and nerve preparations are made, and the minimal stimuli for both nerve and muscle are determined. The muscle of one preparation, A, is placed in a watch-glass filled with normal tap-water saline solution saturated with strychnine (1 in 6700); the nerve is left outside upon a piece of wet filter-paper. The nerve of preparation B is placed in the solution, but its muscle is placed outside upon the filter-paper.

The minimal stimuli are determined from time to time, and it will be found that the endings of the nerve in the muscle exposed to the strychnine are paralysed. Stimulation of the nerve A produces no contraction, but direct stimulation of the muscle readily evokes a response. In this respect strychnine resembles curare (see Expt. XLVIII.).

Hydrastine

Hydrastis canadensis, yellow root or golden seal, is a small herbaceous perennial, indigenous to most parts of the United States and Canada; it belongs to the Ranunculaceæ. Hydrastine is one of the alkaloids found in the rhizome of the plant; it is a colourless, crystalline substance, almost insoluble in water; its formula is $C_{21}H_{21}NO_6$.

The hydrochlorate of hydrastine is readily soluble in water, and on this account is most suitable for experiments.

Experiment XXXIV.—*The Effects of Poisonous Doses.*—The cerebral hemispheres of a frog are destroyed in the way already described[1]; then 81 decimilligrammes ($\frac{1}{8}$ grain) dissolved in 0·592 c.c. (10 ♏) of tap-water saline solution are injected by a hypodermic syringe under the skin of the back. Within about ten minutes the muscles will begin to twitch and then convulsions will follow. The body during a spasm is rigid and rests on the mouth and toes of the hind limbs; this posture is known as *emprosthotonus*. When the spasm has ceased, another can be evoked by touching or blowing upon the skin. The excitability of the spinal cord has been so increased that a very slight stimulus is sufficient to produce a general discharge of impulses to the muscles of the body. Paralysis and death of the tissues will soon follow.

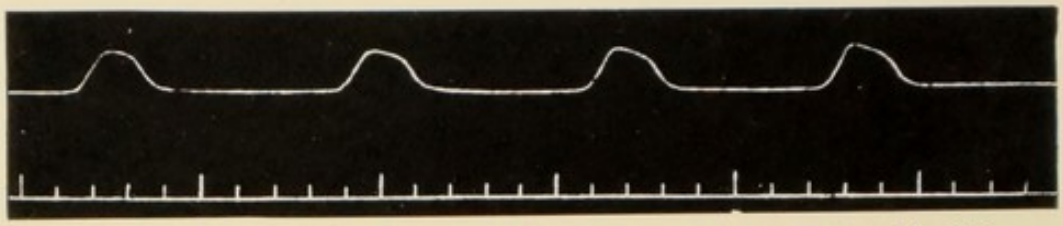
By careful observation the spasms are found to be composed of a rapid series of contractions, incomplete tetanus or *tonus*, followed after a pause by a series of prolonged twitches

[1] P. 2.

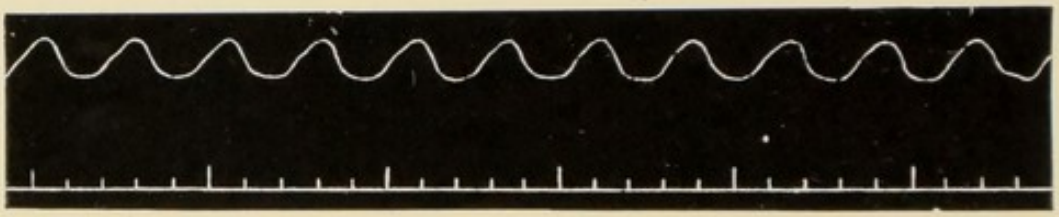
or *clonus*. These will be recorded graphically in a later experiment.

A smaller dose will produce the characteristic effects, but if the frog be kept moist in a plate full of water and covered by a bell-jar for a day or two, recovery may occur. The drug is excreted by the kidneys.

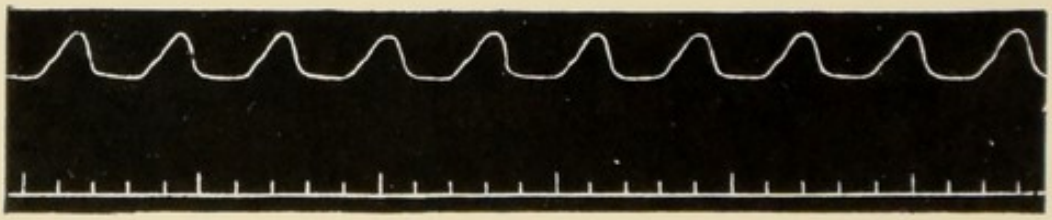
EXPERIMENT XXXV.— *The Effect upon the Heart.*— A preparation of the heart of a normal frog is made, and the con-



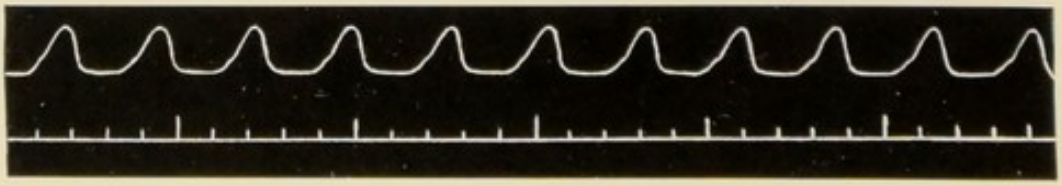
A few drops of solution of hydrastine hydrochlorate in tap-water, 1 in 200, painted on sinus. Curve taken twenty-five seconds later.



A few drops of solution of hydrastine hydrochlorate in tap-water, 1 in 200, painted on auricles. Curve taken twenty-five seconds later.



A few drops of solution of hydrastine hydrochlorate in tap-water, 1 in 200, painted on ventricle. Curve taken twenty-five seconds later.



Before the application of the drug. The time is marked in seconds.

FIG. 30.—Contraction of the heart of a frog. These curves show that hydrastine acts chiefly upon the sinus.

tractions are carefully observed and recorded upon a slowly

revolving drum; then a few drops of tap-water saline solution are applied by a small pipette to the heart, and the effect, if

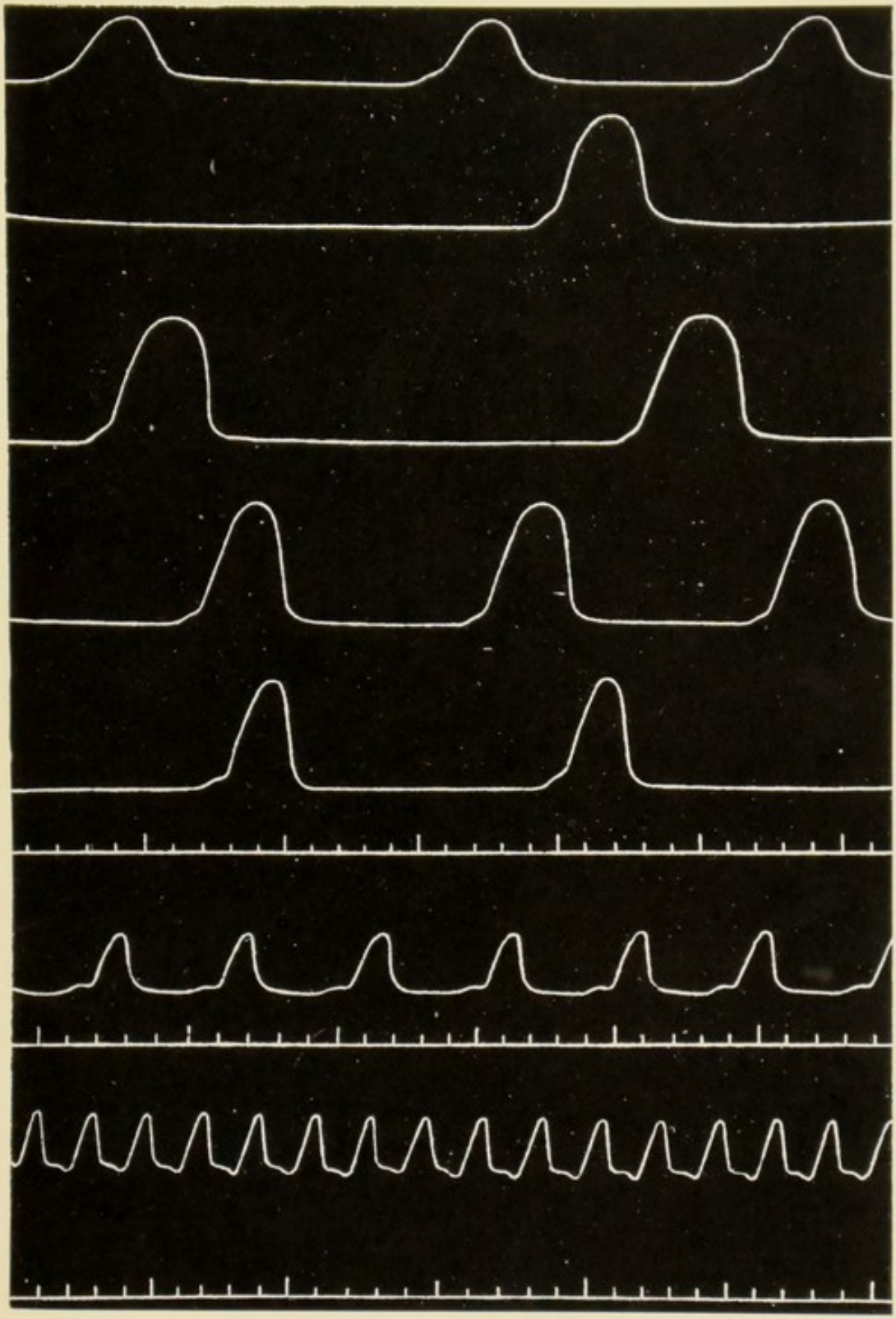


FIG. 31.—Contraction of the heart of a frog. The effect of hydrastine hydrochloride. Curve I. is the normal. The remaining curves show the effect of increased doses of the drug. The time is marked in seconds.

any, is recorded. Two or three drops of a solution containing 1 part of hydrastine hydrochlorate in 200 parts of saline

are applied to the ventricle and a further record is taken. Now the sinu-auricular junction of the heart is treated in the same way, and a prompt effect will be observed (Fig. 30). The rate of the heart's contraction is diminished, but the force and duration are augmented; thus in one experiment there were two contractions in fifteen seconds as compared with two in four seconds before the application of the drug, and the duration and force of the ventricular contraction were more than doubled. The curves (Fig. 31) illustrate these points.

EXPERIMENT XXXVI.—*The Effect upon the Inhibitory Power of the Vagus.*—In a pithed frog the vagus nerve is exposed by the dissection elsewhere described,[1] and a small pair of electrodes are placed under it. The rate of the contraction of the heart is observed, and then a strong faradising

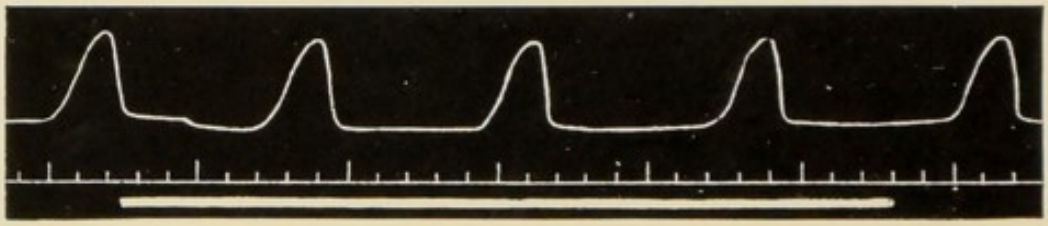


FIG. 32.—Contraction of the frog's heart. Stimulation of the vago-sympathetic nerve after the action of hydrastine hydrochlorate. The time is marked in seconds.

current is passed through the electrodes for a second or two. The heart beats much more slowly or ceases to beat. After the heart has recovered, two or three drops of a solution containing 1 part of hydrastine hydrochlorate in 200 parts of saline are placed upon the junction of the sinus and auricle. The effect is a slower and more forcible beat. An interrupted current of the strength previously used is again passed through the electrodes; the heart is *not* inhibited. If the electrodes be now applied to the crescentic groove[2] and the current passed, the heart will cease to beat. The drug paralyses the endings of the vagus around the ganglia of the heart.

The curve (Fig. 32) is a graphic record of such an experiment.

[1] P. 5. [2] P. 12.

Experiment XXXVII. — *The Effect upon the Nervous System.* — It has already been mentioned that poisonous

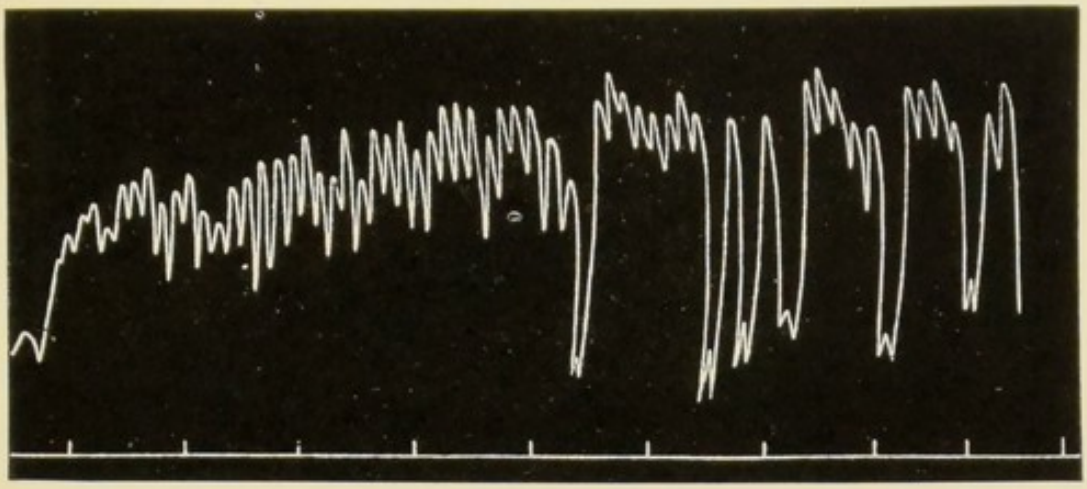


Fig. 33. — Incomplete tetanus of the gastrocnemius muscle produced in a brainless frog by the action of hydrastine hydrochlorate. The time is marked in seconds.

doses of the drug produce convulsions, and that the excitability is so much increased that a slight touch or puff of

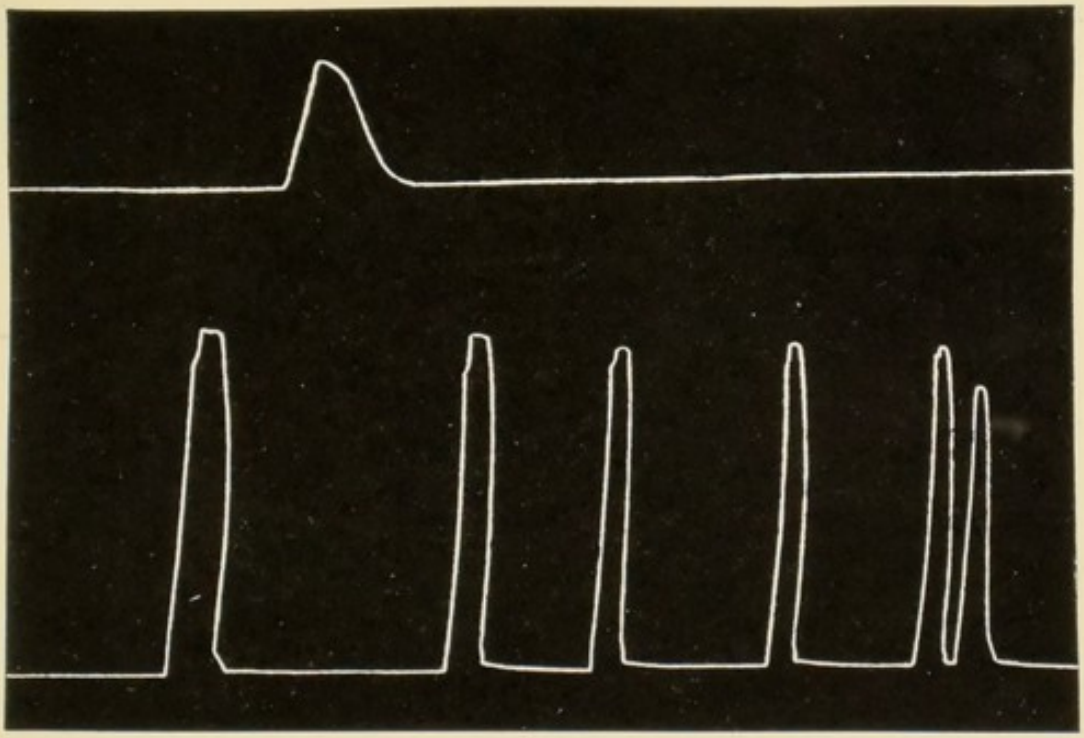


Fig. 34. — Clonic contractions of the gastrocnemius muscle produced in a brainless frog by the action of hydrastine hydrochlorate. This is a continuation of the tracing (Fig. 33), and its duration is the same, ten seconds ; the contractions are few but prolonged.

wind suffices to send the frog into convulsions. The seat of origin of these convulsions can be traced by the following

experiment. In a brainless frog the gastrocnemius muscle is prepared in such a way that the circulation of blood remains intact.[1] The body of the frog is fixed by a piece of moist flannel fastened by pins to the cork of the myograph, and the gastrocnemius muscle is connected with the lever; when everything is in working order, 81 decimilligrammes ($\frac{1}{8}$ grain) of the drug dissolved in 0·592 c.c. (10 ♏) of tap-water saline solution are injected under the skin of the back. In about ten minutes the muscle will begin to twitch, then an incomplete tetanus will be recorded, and, if the time be marked in seconds, the rate of contraction will be seen to be from eight to ten per second. The tonic contractions will soon cease, and there will occur well-marked twitches, clonus. The final result is paralysis and death of the tissues.

If the spinal cord be destroyed by a probe during the stage of incomplete tetanus the contractions will cease at once, showing that the contractions were due to the action of the drug upon the nerve-cells and dendrites in the spinal cord.

Experiment XXXVIII.—*The Effect upon Muscle and Nerve.* —From a pithed frog two muscle and nerve preparations are made, care being taken to obtain the entire length of the sciatic nerve. The minimal stimuli for direct and indirect excitation are determined, and then the muscle of preparation A is placed in a watch-glass full of a solution of hydrastine hydrochlorate, 1 in 200 parts of tap-water saline solution, but the nerve is kept outside upon a moist piece of glass or filter paper; in the case of preparation B the nerve is placed in the solution of the drug, but the muscle is left outside. Stimulation of the nerve A will soon fail to produce a contraction, but direct excitation will make the muscle contract. Excitation of the nerve B produces a contraction of its muscle. Soon the muscle A will become more opaque in appearance and will fail to respond to the strongest stimulus. The nerve B will retain

[1] P. 37.

the power of evoking a contraction in its muscle for a considerable time.

These experiments show that the drug acts first upon the terminations of the nerves in the muscle and then upon the muscle-substance itself.

Morphine

Morphine, $C_{17}H_{19}NO_3 \cdot H_2O$, is an alkaloid prepared from opium, the inspissated juice of the poppy, *Papaver somniferum*. It is a colourless, crystalline substance, with a bitter taste and an alkaline reaction; it is slightly soluble in cold water.

On account of their greater solubility the salts of morphine will be used in the following experiments. One part of the hydrochlorate, $C_{17}H_{19}NO_3HCl \cdot 3H_2O$, is soluble in 24 parts of water at 15°; the solubility of the acetate, $C_{17}H_{19}NO_3 \cdot C_2H_4O_2$, is 1 part in $2\frac{1}{2}$ parts of water.

Experiment XXXIX.—*The Effects of Poisonous Doses.*—Under the skin of a brainless frog are injected 10 minims (0·592 c.c.) of a saturated solution (about 4 per cent.) of morphine hydrochlorate in normal tap-water saline sclution. No effect will be observed, for the frog is very tolerant of morphine.

If a dose of 15 minims (0·888 c.c.) of a 10 per cent. solution of morphine acetate in normal tap-water saline solution be injected under the skin of a brainless frog, poisonous effects will be quickly observed. Within five minutes the frog becomes sluggish, cannot jump well, and does not readily turn over if it be placed on its back. Ten minutes later the frog will be lying with its limbs extended, and will be unable to jump or move in a co-ordinated manner; reflex movements will be present, but will soon be less marked. Respiration ceases, all reflexes are abolished, the circulation of the blood in the web of a foot examined under the low power of a microscope will have ceased, and the frog dies.

A smaller dose, 5 minims (0·296 c.c.), will abolish all reflex movement, but, if the frog be kept moist in a plate of

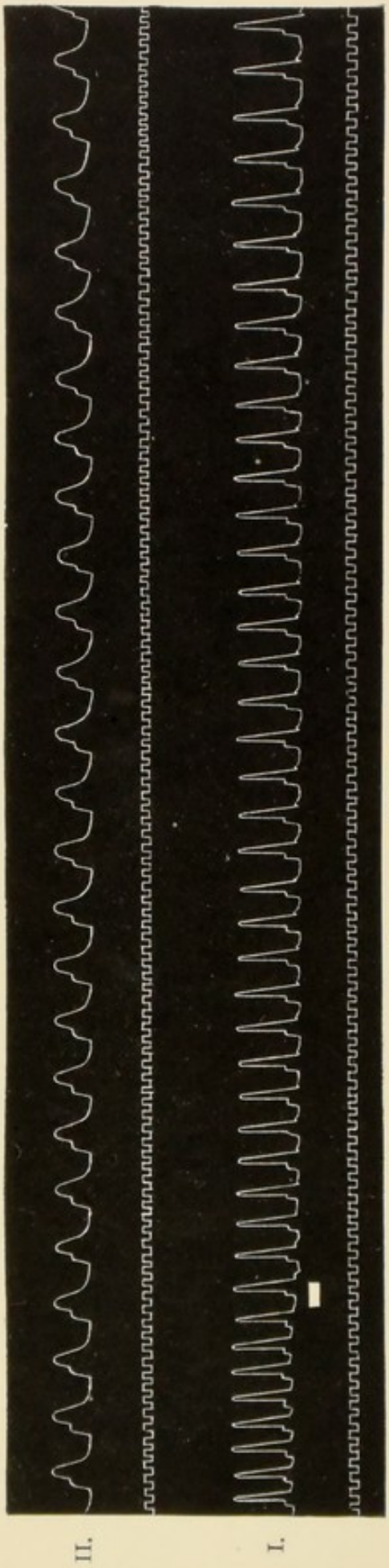


FIG. 35.—Contraction of the frog's heart. I. The heart, which had been previously moistened with normal tap-water saline, was, at the point marked, treated with several drops of a saturated solution of morphine acetate (about 40 per cent.) in normal tap-water saline. II. Curve from another heart after the prolonged action of the drug. The time is marked in seconds.

water, covered by a bell-jar, the reflex power will gradually return. The excitability will become abnormally increased, so that a slight touch will cause violent convulsions resembling those produced by strychnine (see Expt. XXX.). From these effects of the drug the frog may recover in several hours.

EXPERIMENT XL.—*The Effect upon the Nervous System.*—The foregoing experiments have shown that morphine depresses the excitability of the central nervous system, and in large doses produces paralysis and death. After non-lethal doses the stage of depression is succeeded by one of greatly increased excitability.

Morphine has little or no direct effect upon the nerve fibres (see Expt. XLII.).

EXPERIMENT XLI.—*The Effect upon the Heart.*—Small doses of morphine have little or no effect upon the heart of the frog; in this experiment, therefore, a strong solution of the acetate will be used.

Records are taken of the contraction of the heart before,

and after, the application of a few drops of normal tap-water saline solution. Then the vago-sympathetic nerve is stimulated with a strong faradising current, and the inhibition and the after-effect are recorded. Several drops of a saturated solution (about 40 per cent.) of morphine acetate in normal tap-water saline solution are applied to the heart. The beat becomes slower, and if further doses be given from time to time the heart will contract and dilate more slowly and feebly (Fig. 35, Curves I. and II.). Stimulation of the vago-sympathetic nerve is still effective.

EXPERIMENT XLII.—*The Effect upon Muscle and Nerve.*—Two muscle and nerve preparations are made, and their excitability is measured by a determination of the minimal stimuli. The nerve of preparation A and the muscle of preparation B are placed in a watch-glass filled with normal tap-water saline solution saturated with morphine acetate. From time to time the excitability of the muscles and nerves is determined. Little or no change will be observed, if precautions be taken[1] to prevent drying of the tissues. Muscle and nerve are not affected by morphine.

Caffeine

Caffeine, $C_8H_{10}N_4O_2 \cdot H_2O$, is an alkaloid generally prepared from the dried leaves of *Camellia thea*, or from the dried seed of *Coffea arabica*. It is a colourless, silky, inodorous, crystalline substance soluble in 80 parts of cold water.

Coffee contains caffeine. The active principle of tea was formerly known as theine, but it has been proved to be identical with caffeine; tea also contains theophylline.

EXPERIMENT XLIII.—*The Effects of Poisonous Doses.*—Under the skin of a brainless frog are injected 10 minims (0·592 c.c.) of a saturated solution of caffeine in normal tap-water saline solution. The immediate effect is a stage of great excitement.

See p. 16.

Within five minutes this is followed by rigidity of some of the limbs, which may persist for an hour or two; this rigidity passes off when the stage of paralysis begins. The reflexes are then entirely absent, and the frog is apparently dead. If, however, it be kept in a plate filled with water, and covered by a bell-jar, the paralysis will gradually disappear and the frog will recover from the effects of the drug in about twenty-four hours.

EXPERIMENT XLIV.—*The Effect upon the Heart.*—A record of the contraction of the heart is taken, and after the effect, if there be any, of the application of normal tap-water saline solution has been recorded, a few drops of the fluid saturated with caffeine (about 1 part in 80) are placed upon the heart. There is a marked effect. The tone of the cardiac muscle is increased, and the heart only relaxes slightly during the diastole of the ventricle (Fig. 36, Curve I.). Further doses of the drug are applied; the beat becomes slower and the ventricle contracts so feebly that the auricular contraction may be the higher (Fig. 36, Curves II. and III.). The further action of the drug will cause rigor of the ventricle, but the pulsation of the sinus and of the auricles may continue for several minutes after this stage.

The vago-sympathetic nerve is not paralysed by the prolonged action of the drug (Fig. 36, Curve III.).

Caffeine acts most quickly upon the ventricle of the heart. If the heart of a pithed frog be excised and placed in a watch-glass filled with normal tap-water saline saturated with caffeine, the contractions are at first quickened; the ventricle contracts more and more feebly, and then ceases to beat; the auricles may still give a powerful contraction from time to time.

EXPERIMENT XLV.—*The Effect upon Muscle and Nerve.*—Two muscle and nerve preparations are made, and the minimal stimuli for the nerves and muscles are determined.

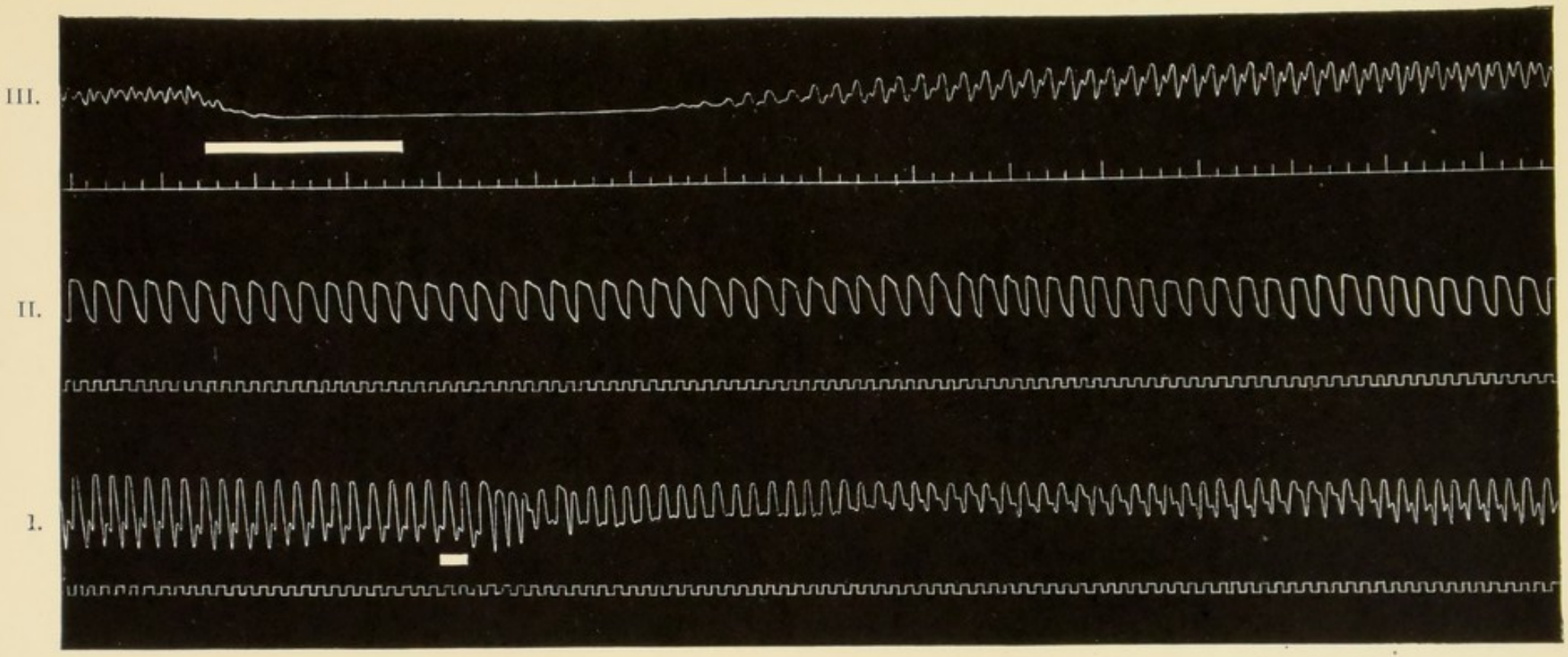


FIG. 36.—Contraction of the frog's heart. I. Begin with normal tap-water saline solution ; at the point marked a few drops of a saturated solution (1 in 80) of caffeine were applied. II. Continuation of I. after the further action of the drug. The first and higher contraction is due to the auricle. Rigor of the ventricle is beginning. III. From another heart. Late effect of the drug. The first and higher contraction is due to the auricle. Stimulation of the vago-sympathetic during the time marked by the white line. The heart is inhibited ; the after-effect is an improvement of the ventricular contraction. The time is marked in seconds.

The muscle of preparation A and the nerve of preparation B are placed in tap-water saline solution, saturated with caffeine (about 1 in 80). The minimal stimuli are again determined. The muscle under the influence of the drug contracts, becomes white and rigid, and in a few minutes fails to respond to the strongest stimulus; the caffeine has caused rigor. The excitability of the nerve exposed to the drug is increased and is retained for a long time.

It will be observed that this action of caffeine upon muscle is also shown in the case of the heart (Expt. XLIV.).

Experiment XLVI.—*The Effect upon the Nervous System.*—The results of the first experiment with caffeine show that it increases the excitability of the central nervous system. This stage of excitement is followed by one of deep depression and the abolition of all reflex movements. Recovery slowly takes place.

The excitability of nerve is increased by the direct action of caffeine.

Curare

Curare (Woorari or Urari) is a poisonous compound prepared from various plants of the genus Strychnos, and used as an arrow-poison by some of the savage tribes of South America. It is a brown amorphous substance, and contains an alkaloid curarine, $C_{10}H_{15}N$, which is soluble in water.

Experiment XLVII.—*The Effects of Poisonous Doses.*—Under the skin of the back of a brainless frog are injected 2 minims (0·118 c.c.) of a 1 per cent. solution of curare in normal tap-water saline. Within about five minutes the frog will become completely paralysed and will lie outstretched in a toneless condition; there will be an absence of respiratory movements and of reflexes. Direct stimulation of the muscles by an electric current will produce a contraction. An examination of the web of the foot with the low power of a

microscope will show that the circulation soon ceases and the frog will die.

A smaller dose will produce complete paralysis, but if the frog be kept moist in a plate full of tap-water and covered by a bell-jar, respiration can be maintained by the skin, and recovery from the effects of the drug may occur in a day or two. The curare is excreted by the kidneys, and the urine of the frog will produce the characteristic effects of the drug if it be injected into another frog. After the injection of non-lethal doses an excessive accumulation of lymph under the skin of the legs is sometimes observed.

If curare be given by the mouth it is excreted so quickly by the kidneys that poisonous results do not obtain.

Experiment XLVIII.—*Effect upon Muscle and Nerve.*—(*a*) The gastrocnemius muscle with the entire length of the sciatic nerve is prepared upon each side of a pithed frog. The minimal stimuli necessary to excite the muscle and nerve of each preparation are determined. The muscle of preparation A is then placed in a watch-glass full of a 1 per cent. solution of curare in normal tap-water saline solution, but the nerve is placed outside upon a glass-slide moistened with normal tap-water saline solution. The nerve of preparation B is placed in another watch-glass containing a similar solution of curare, but the muscle is left outside. In a few minutes a strong single induction-shock is applied to the nerve A; the muscle does not contract, but direct stimulation of the muscle produces a response. A weaker stimulus is now applied to the nerve B; the muscle contracts.

These experiments show that the drug paralyses the terminations of the nerve in the muscle. The excitability of the muscle is somewhat diminished owing to the direct action of the drug upon the muscle-substance itself.

(*β*) The cerebral hemispheres of a frog are destroyed, and the sciatic nerve is exposed on each side. A strong ligature is now passed under the right sciatic nerve and is tightly tied

around all the remaining structures of the thigh, in order to completely stop the circulation of the blood in the right leg. Examination of the web of this foot with the low power of a microscope should show that the stream of blood has ceased to flow. Stimulation of either sciatic nerve by an induction-shock will produce a contraction in the muscles it supplies. Under the skin of the back is now injected 1 minim (0·059 c.c.) of a 1 per cent. solution of curare. In a few minutes there will be marked paralysis, and stimulation of the left sciatic nerve will no longer produce a contraction; stimulation, however, of the right sciatic nerve will produce a contraction, for the poison in the blood has been prevented by the tight ligature from entering the muscles of the right leg. The muscle substance itself is still excitable in the leg exposed to the action of the drug, for the application of the electrodes directly to the left gastrocnemius will produce a contraction. The nerve-trunk on each side has been exposed to the action of the poison, and, as the previous experiment showed, is not affected thereby; the muscle is excitable on each side; the block in the nervous impulse must therefore be in the terminations of the left sciatic nerve in the muscle. This effect is the characteristic one of curare.

Experiment XLIX.—*The Effect upon the Nervous System.*—The previous experiments show that the characteristic action of curare is to paralyse the terminations of the motor nerves, and thus produce general paralysis. The general excitability of the central nervous system is also lowered; this is shown by the following experiment. Into a brainless frog is injected 1 minim (0·059 c.c.) of a 1 per cent. solution of curare. The general excitability will soon become much diminished, and well-marked signs of the commencement of paralysis will be observed. If 1 minim (0·059 c.c.) of a saturated solution of strychnine (1 in 6700) in normal tap-water saline be injected at this stage, the excitability of the central nervous system will be increased or even raised above that of the

normal. The strychnine has counteracted the depression produced by the curare.

The next experiment shows that large doses of curare paralyse the vagus nerve.

Experiment L.—*The Effect upon the Heart.*—A record of the contraction of the heart is taken both before and after the application of a few drops of normal tap-water saline solution. The vago-sympathetic nerve is stimulated with a strong faradising current, and the inhibition and after-effect are recorded (Fig. 37). These portions of the tracing will serve as controls for the investigation of the action of the drug. Several drops of a solution of 1 part of curare in 100 parts of normal tap-water saline solution are applied to the heart, and this dose is repeated from time to time during the record of the beat. At first (Fig. 38, Curve I.) it will be possible to inhibit the heart by strong stimulation of the vago-sympathetic nerve, but after a large dose no effect, beyond an acceleration, is observed (Fig. 38, Curves II. and III.). The pre-ganglionic endings of the

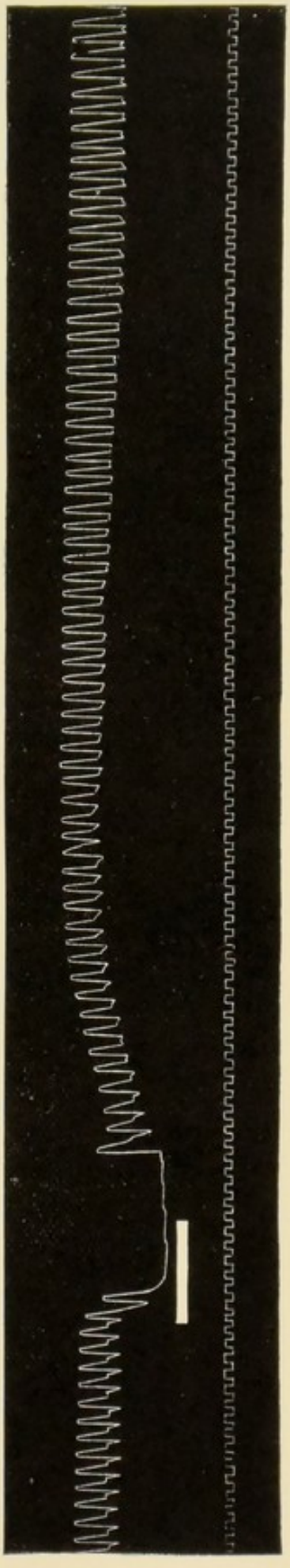


Fig. 37.—Contraction of the heart of a frog. Strong faradisation of the vago-sympathetic nerve was maintained during the time marked by the horizontal line. There is a period of delay, then inhibition, which persists for two or three seconds after the stimulation. This is followed by the characteristic after-effect. The heart had been moistened only with normal tap-water saline solution. The time is marked in seconds. The continuation of this experiment is found in Fig. 38.

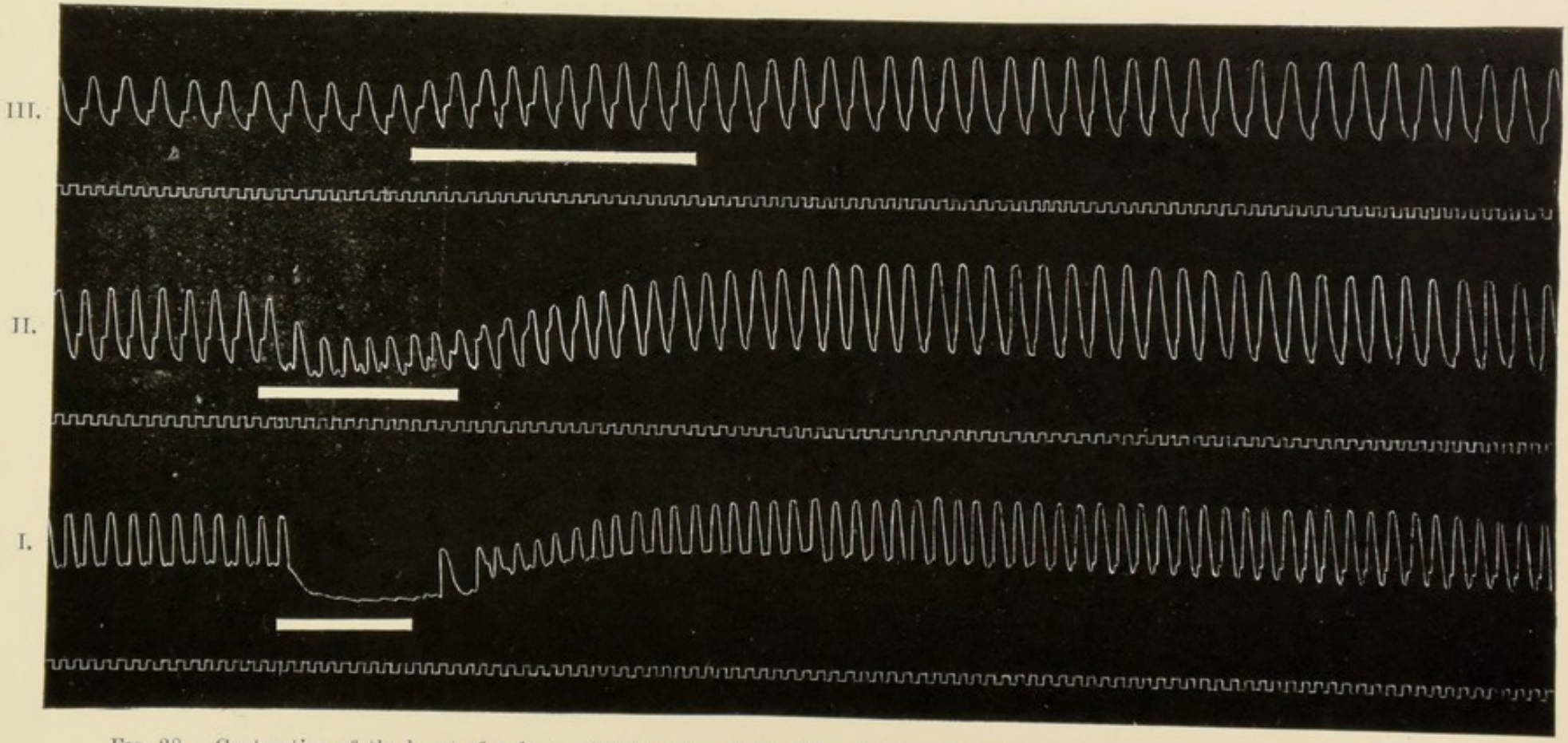


FIG. 38.—Contraction of the heart of a frog. Continuation of Fig. 37. I. Heart had been moistened with a 1 per cent. solution of curare in normal tap-water saline one minute and a half before the vago-sympathetic nerve was stimulated. II. Stimulation of the vago-sympathetic nerve after a further dose of the drug. III. Stimulation of the vago-sympathetic nerve after prolonged action of the drug. The duration of the stimulation is shown by the horizontal line. The time is marked in seconds.

vagus nerve are paralysed, but not the post-ganglionic fibres of the sympathetic. Stimulation of the sinus will still inhibit the heart-beat, until a dose strong enough to paralyse the post-ganglionic fibres of the vagus is given.

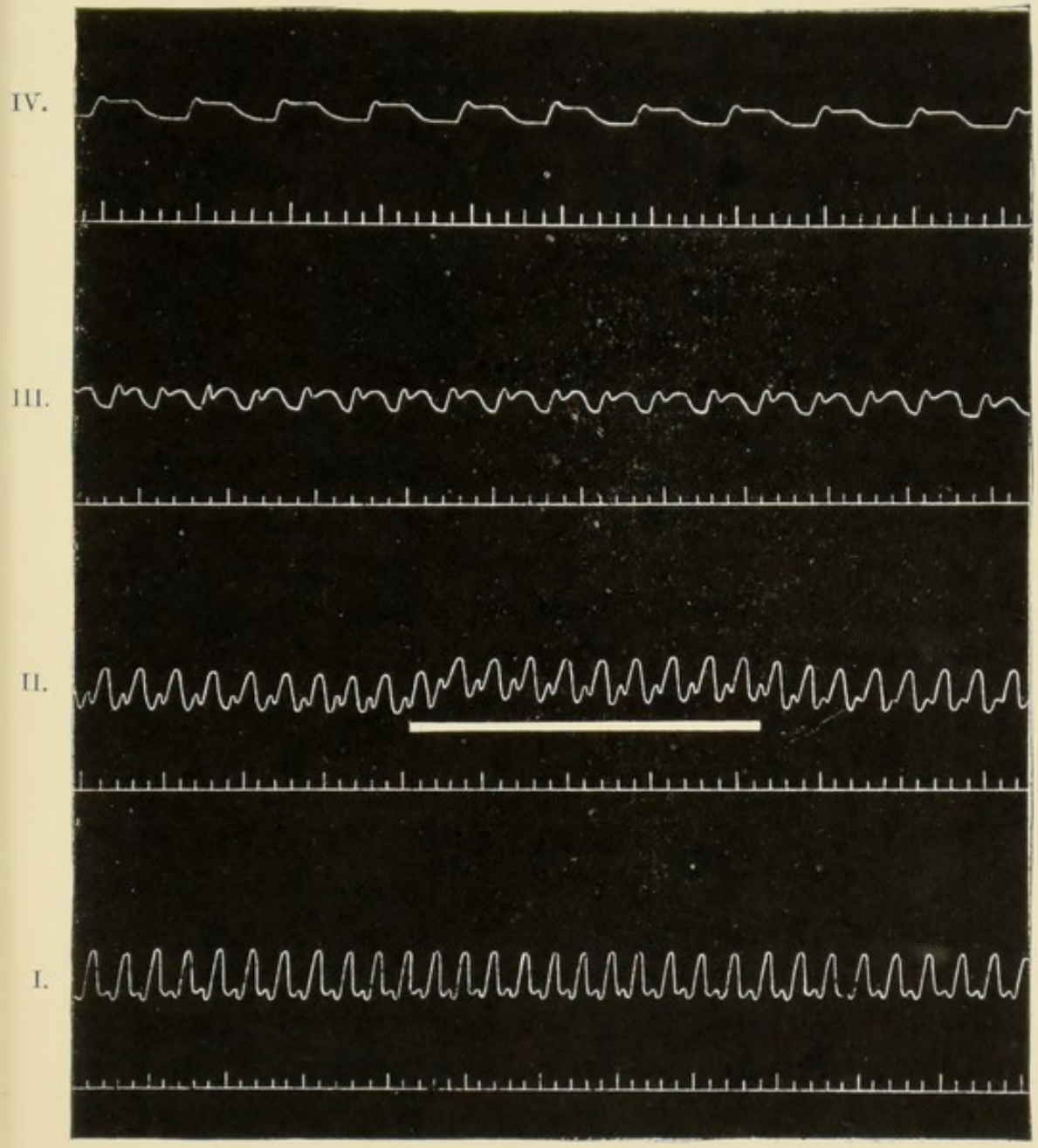


FIG. 39.—Contraction of the heart of a frog. I. This is the normal contraction before the application of curare. II. Stimulation of the vago-sympathetic nerve after the continued action of the drug. There is no inhibition. The slight rise in the base line is due to an escape of current, which stimulated the muscles of the floor of the mouth. III. and IV. Later effect of curare; the contractions are slower, and the auricular contraction becomes higher than that of the ventricle. The time is marked in seconds.

The heart-beat becomes slower and feeble under the further action of the drug, and this effect is especially

marked in the ventricle; the auricular contraction becomes higher than that of the ventricle (Fig. 39, Curves III. and IV.).

There is a marked contrast between curare and atropine: small doses of the former quickly paralyse the endings of motor nerves, whereas atropine can only effect this when it is applied in large doses and for a considerable time. The endings of the vagus nerve are quickly paralysed by small doses of atropine, but the same result only obtains after the prolonged action of large doses of curare.

Nicotine

Nicotine, $C_{10}H_{14}N_2$, is a volatile liquid alkaloid present in tobacco as a malate, and obtained therefrom by distillation with an alkali. Pure nicotine is colourless and has little odour, but, if it be kept for some time, it becomes dark brown in colour, and acquires the characteristic odour of tobacco. It has a strongly alkaline reaction, a specific gravity of 1·027, and is readily soluble in water.

Experiment LI.—*The Effects of Poisonous Doses.*—Under the skin of the back of a brainless frog are injected 10 minims (0·592 c.c.) of a solution containing 1 part of nicotine in 20 parts of tap-water saline solution. At once there is a stage of excitement, followed within a minute by tonic contraction of the front limbs and twitches in the hind limbs. The rigidity of the front limbs persists. A slight touch or a puff of wind may now send the frog into tetanus similar to that seen with strychnine. Paralysis follows in about fifteen minutes after the injection, and no reflex movements can be obtained even with the strongest stimulus. Recovery does not occur even if the frog be kept in shallow water for a day or two. An examination of the heart shows that the ventricle is firmly contracted, but the auricles are engorged with very venous blood.

A dose of 5 minims (0·296 c.c.) of a 1 per cent. solution

of nicotine will produce poisoning from which the frog may recover, if precautions be taken to keep it moist.

This and the following experiments show that nicotine acts chiefly on the central nervous system, the sympathetic ganglia, and the terminations of nerve-fibres.

Experiment LII.—*The Effects upon the Heart.*—The vago-sympathetic nerve is exposed upon one side of a pithed frog, and the heart is connected with the cardiograph in the ordinary manner. A tracing of the heart's beat before and after it has been moistened with normal tap-water saline solution is taken as a control, and then the vago-sympathetic nerve is stimulated with a strong tetanising current. The heart ceases to beat. Two or three drops of a solution containing 1 part of nicotine in 1000 parts of normal tap-water saline solution are now allowed to flow over the heart. The record is continued during this application of the drug, and in two or three minutes the heart shows a slower but somewhat more prolonged contraction. Stimulation of the vago-sympathetic nerve with the same strength of current as that previously used will now cause no inhibition of the heart-beat; there may even be an acceleration due to the stimulation of the sympathetic fibres. The pre-ganglionic terminations of the vagus nerve have been paralysed.

Direct stimulation of the sinus at this stage will stop the heart-beat (Fig. 41), but if a further dose be given the contraction becomes more prolonged, less frequent and less powerful, and stimulation of the sinus will now quicken the heart-beat; on the cessation of the stimulation the heart will cease to beat for several seconds (Fig. 42, Curve I.), or even for a minute (Fig. 42, Curve II.). The prolonged action of the nicotine has paralysed all the nervous elements of the heart, which therefore responds to stimulation of the sinus with a series of beats.

The effect of nicotine upon the heart varies according to the dose; with solutions of 1 in 1000 or 1 in 500 parts of normal tap-water saline, the beats become slower but more forcible (Fig. 41, and Fig. 40, Curve I.). A stronger solution,

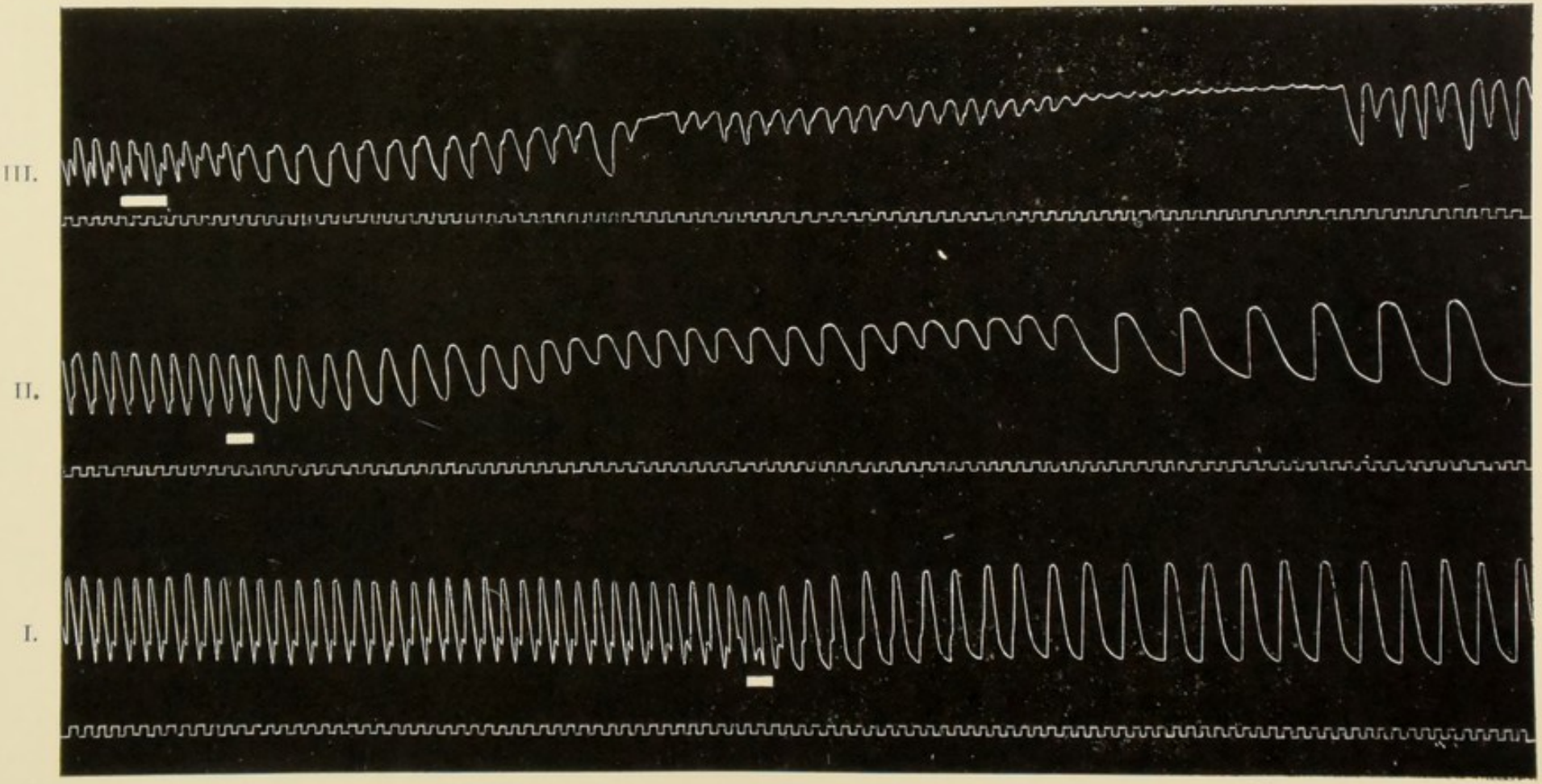


FIG. 40.—Contraction of the frog's heart. I. Heart (*a*) treated with normal tap-water saline, and then at the point marked with a drop or two of nicotine solution, 1 in 500. II. Heart (*b*) treated with normal tap-water saline, and then at the point marked with a drop or two of nicotine solution, 1 in 100. III. Heart (*c*) treated with normal tap-water saline, and then at the point marked with two or three drops of nicotine solution, 1 in 100. The time is marked in seconds.

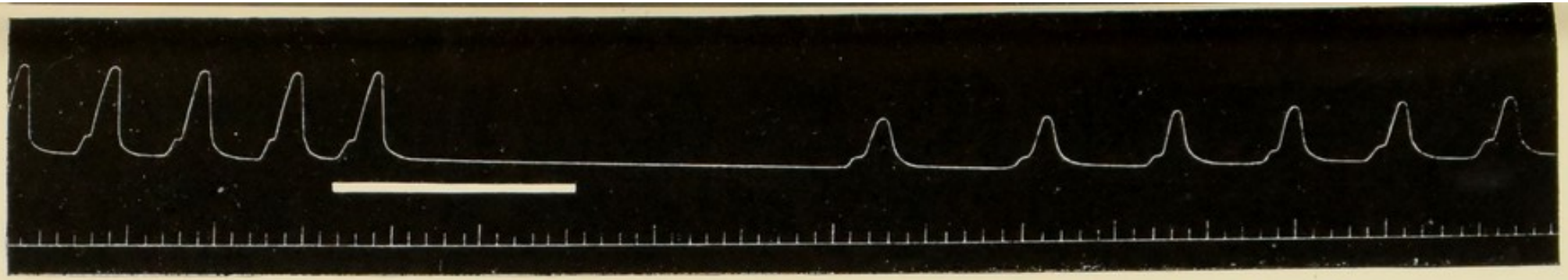


FIG. 41.—Contraction of the heart of a frog. The earlier stage of the effect of nicotine, 1 in 1000 parts of normal tap-water saline solution. The sinus was stimulated with a faradising current during the period marked by the white line. Temperature of the air = 10°. The time is marked in seconds.

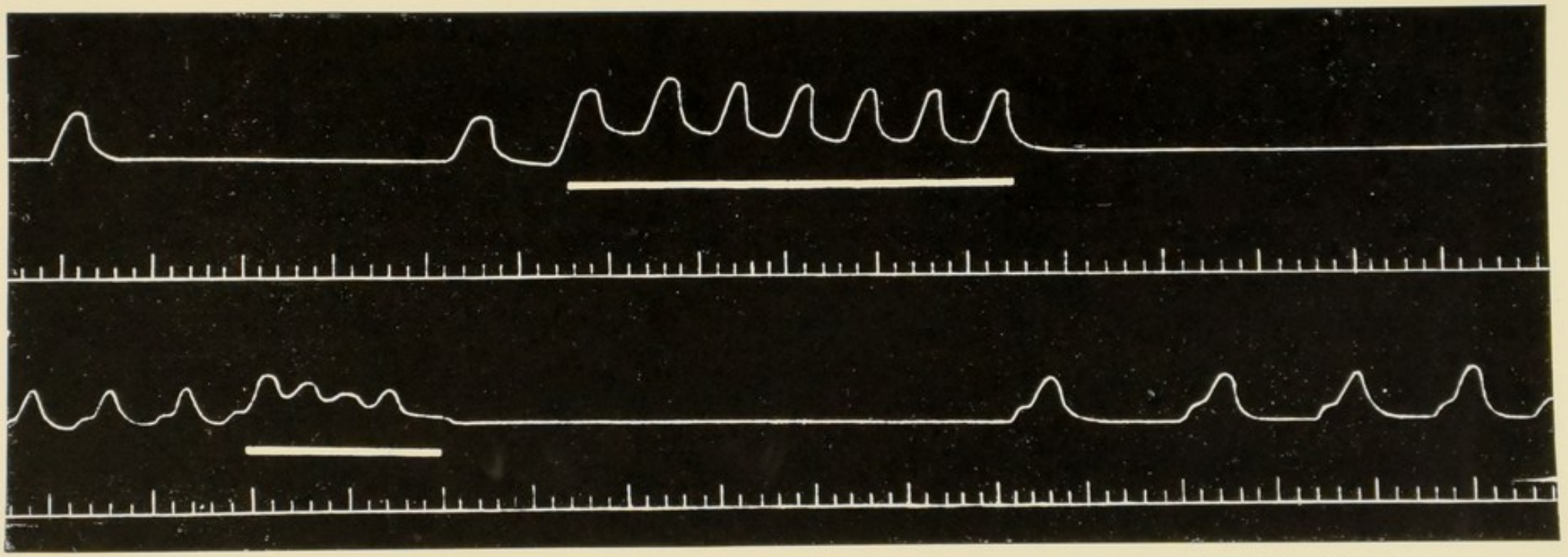


FIG. 42.—Contraction of the frog's heart. I. The later effect of nicotine, 1 in 1000. The sinus was stimulated with a strong faradising current during the period marked by the white line. II. The later effect of nicotine, 1 in 1000. The sinus was stimulated with a strong faradising current during the period marked by the white line. The heart did not commence to beat again until a minute after the cessation of the stimulation. The time is marked in seconds.

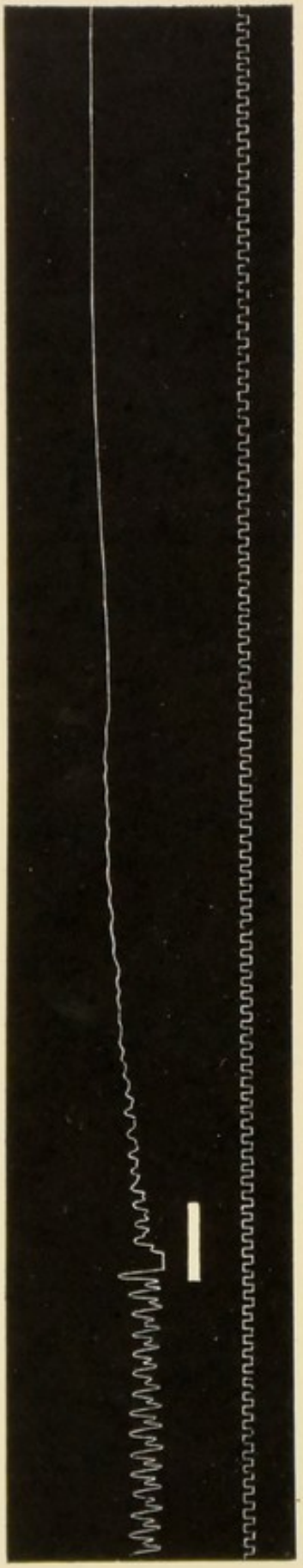


FIG. 43.—Contraction of a frog's heart. At the point marked by the white line a drop of pure nicotine was placed on the heart. The heart quickly ceased to beat, and passed into a rigid and contracted condition. The time is marked in seconds.

1 in 100, produces a marked increase in the tone of the heart; the beats are slower and the heart relaxes but slightly in the intervals between the pulsations; this can be easily observed by the naked eye, and is well shown in the Curves II. and III. of Fig. 40, where the time-mark serves as a base-line. One drop of pure nicotine causes the heart to rapidly pass into a rigid and contracted condition, and all pulsation and excitability are abolished; the heart is dead (Fig. 43).

EXPERIMENT LIII.—*The Effect upon the Nervous System.*—The first experiment upon the action of nicotine shows that the drug acts upon the central nervous system, causing at first increased excitability, and then marked depression and paralysis. The terminations of the vagus nerve in the heart are also paralysed (Experiment LII.), and the next experiment will show that the drug resembles curare in its action upon the terminations of motor nerves.

EXPERIMENT LIV.—*The Effect upon Muscle and Nerve.*—Two muscle and nerve preparations are made, and their excitability is tested by a determination of the minimal

stimuli. The nerve of preparation A and the muscle of preparation B are placed in a watch-glass filled with a solution of nicotine containing 1 part of nicotine and 100 parts of normal tap-water saline solution. The muscle of preparation A and the nerve of preparation B are kept upon a piece of moist filter-paper. Within ten minutes there will be first a great loss in excitability on indirect stimulation of the preparation B, then no contraction on stimulation of the nerve B with the strongest induction-current, and a great loss in the excitability of the muscle B to direct stimulation. An examination of the nerve A will show a decrease in excitability; a stimulus about twice as strong as the original stimulus is now necessary to evoke a contraction. Little or no change will be observed in the muscle A.

This experiment shows that nicotine acts most readily upon the terminations of the nerve-fibres, then upon the muscle-substance itself, and finally upon the trunks of the nerves.

Atropine

Atropine, $C_{17}H_{23}NO_3$, is an alkaloid prepared from the root of *Atropa belladonna*, deadly nightshade. It is a colourless, crystalline substance, sparingly soluble in water.

In the following experiments sulphate of atropine will be used on account of its solubility in water.

Experiment LV.—*The Effects of Poisonous Doses.*—Into a brainless frog are injected 10 minims (0·592 c.c.) of a 10 per cent. solution of atropine sulphate in normal tap-water saline. There may be a short stage of increased excitability, but it is followed in a few minutes by a marked loss of tone; the frog lies outstretched, and only responds to a stimulus after a long delay. The reflexes disappear, and the frog lies motionless for several hours. If the frog be kept in a plate of water covered by a bell-jar, recovery from the effects of the drug may occur within twenty-four hours.

Sometimes, during the recovery from the action of smaller doses of the drug, convulsions similar to those produced by strychnine are seen.

Experiment LVI.—*The Effects upon the Heart.*—A preparation of the heart is made; the vago-sympathetic nerve on one side is exposed and a pair of small electrodes are placed under the nerve. A short record of the heart's beat before and after the application of normal tap-water saline is taken for a control; a strong faradising current is passed through the nerve for a few seconds, and the heart stops beating (Fig. 8). When the after-effects of the stimulation have passed off, two or three drops of a 0·2 per cent. solution of atropine sulphate in normal tap-water saline are placed upon the sinus of the heart. The heart-beat is not much altered: it may be slightly slower and larger; a marked effect, however, has been produced upon the vago-sympathetic nerve, for a strong faradising current now produces no inhibition, but an acceleration (Fig. 44, Curve I.). The vagus has been paralysed, but the sympathetic is unaffected. The sinus is now stimulated, but no inhibition is produced; the drug has paralysed the inhibitory mechanism.[1]

Further doses of the drug are applied, with the result that the contraction of the heart, especially of the ventricle, becomes weaker and slower (Fig. 44, Curves II. and III.). The muscle of the heart is affected by the poison.

The antagonistic action of atropine to muscarine will be observed later (Expt. LXVIII.).

Experiment LVII.—*The Effect upon the Nervous System.*—The first experiment upon the action of atropine shows that the drug at first stimulates and then profoundly depresses the central nervous system.

Small quantities of the drug rapidly paralyse the terminations of the vagus nerve (Expt. LVI.).

[1] See p. 97.

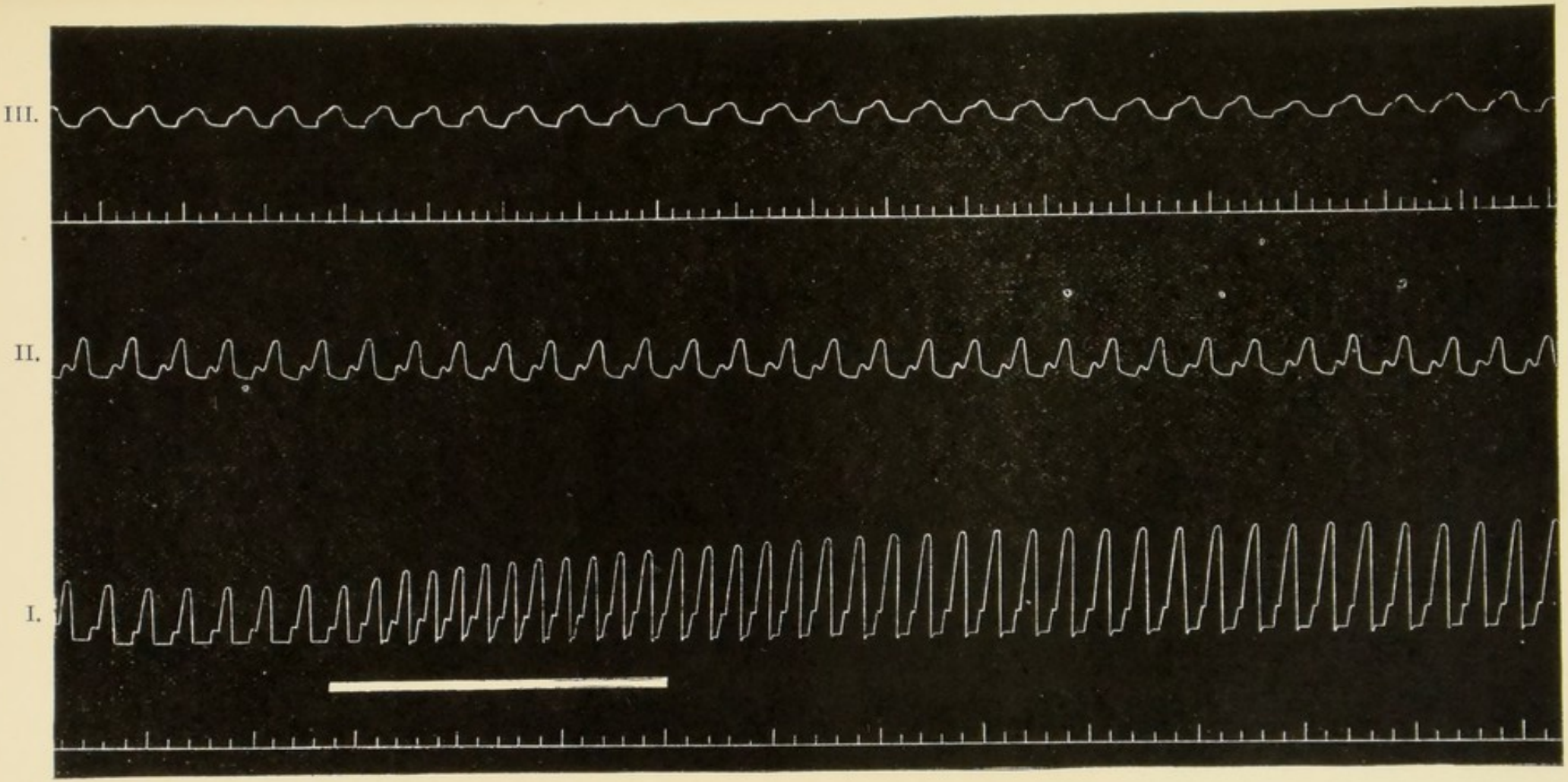


FIG. 44.—Contraction of the frog's heart. I. Six minutes after the application of two or three drops of atropine sulphate, 0·2 per cent. in normal tap-water saline solution. Stimulation of the vago-sympathetic nerve with a strong faradising current produces acceleration. Previously, the same strength of current produced inhibition (Fig. 8). Temperature of air = 20·5°. II. Later effect of atropine. III. Effect of further doses. The time is marked in seconds.

Experiment LVIII.—*The Effect upon Muscle and Nerve.*—Two muscle and nerve preparations are made, and their excitability is determined; the nerve of the one (A) and the muscle of the other (B) are placed in a watch-glass filled with 1 per cent. solution of atropine sulphate in normal tap-water saline. From time to time the excitability of the preparations is determined, but little or no change will be observed even after the tissues have been exposed to the drug for fifteen minutes. Very large doses of atropine will paralyse the terminations of the motor nerves. There is a marked contrast, therefore, between atropine and curare; small doses of the former paralyse the vagus, whereas large doses of the latter are needed to produce that effect; small quantities of curare paralyse the terminations of motor nerves in voluntary muscle, but very large doses of atropine must be applied before similar effects obtain. (See "Curare," p. 55.) Atropine dilates the pupil of the eye by paralysing the terminations of the motor oculi.[1]

Cocaine

Cocaine, $C_{17}H_{21}NO_4$, is an alkaloid obtained from the leaves of cocoa (*Erythroxylon coca*). Its hydrochlorate, $C_{17}H_{21}NO_4 \cdot HCl$, is used in medicine; it is a colourless, crystalline substance readily soluble in water, alcohol, and ether.

Experiment LIX.—*The Effects of Poisonous Doses.*—Under the back of a brainless frog are injected 5 minims (0·296 c.c.) of a 1 per cent. solution of cocaine[2] in normal tap-water saline. The excitability of the central nervous system will be rapidly depressed, and in a few minutes the frog will be completely paralysed. No reflexes will be present, but the heart will continue to beat for some time. Death generally occurs within an hour of the injection.

Smaller doses, 1 to 2 minims, will produce at first an increased excitability, lasting for a few minutes, and then

[1] This effect can be shown by placing a few drops of the solution of atropine sulphate between the eyelids of a rabbit. The dilatation of the pupil thereby produced can be antagonised by physostigmine, muscarine, and pilocarpine. See pp. 75 and 92.

[2] Cocaine hydrochlorate.

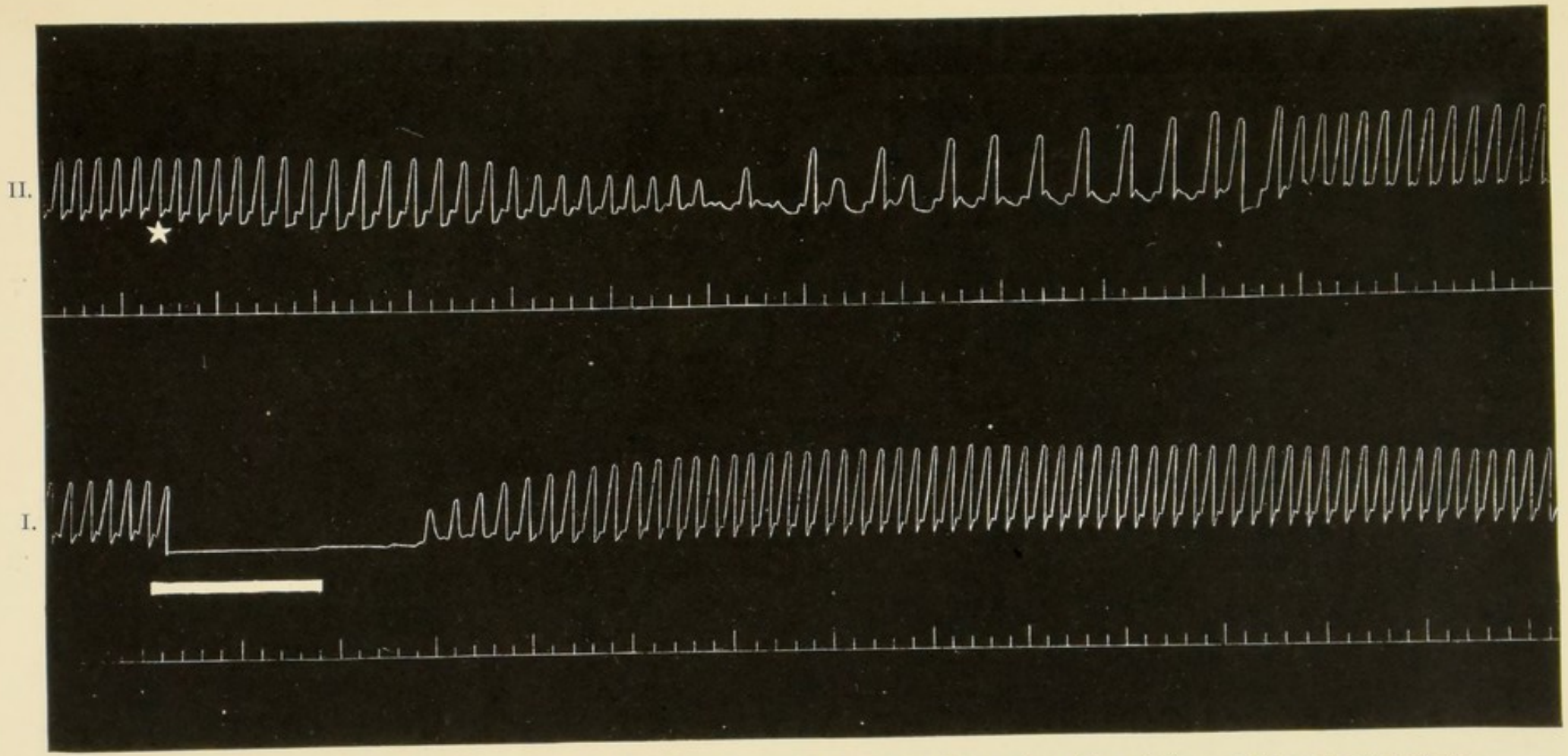


FIG. 45.—Contraction of a frog's heart. I. The heart was moistened with normal tap-water saline solution, and the vago-sympathetic nerve was stimulated with a strong faradising current. II. At the point marked by the star, a few drops of a solution of cocaine, 1 in 500, were applied. The time is marked in seconds.

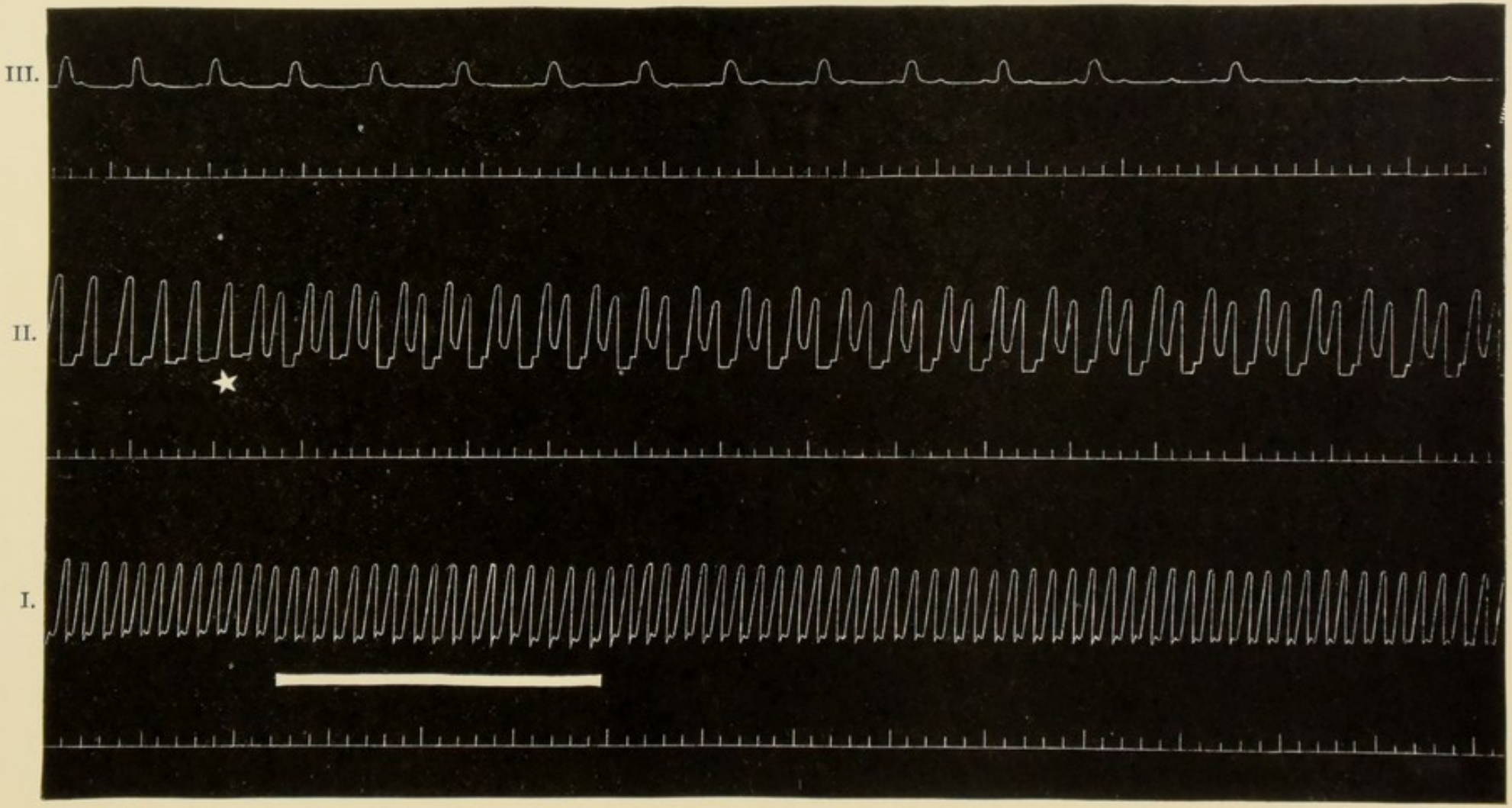


FIG. 46.—Continuation of Fig. 45. I. After the first effects of cocaine had passed off, the vago-sympathetic nerve was stimulated with a strong faradising current: there was no inhibition. II. The effect of the application of a further dose of cocaine. III. After the application of several drops of a 1 per cent. solution of cocaine. The small curves are due to the contraction of the auricles, which is not in each case followed by a contraction of the ventricle. Temperature of air = 28°. The time is marked in seconds.

marked loss of tone and temporary paralysis; the frog may recover in about twelve hours if it be kept moist in a plate full of water and covered with a bell-jar.

Experiment LX.—*The Effect upon the Heart.*—A preparation of the heart and vago-sympathetic nerve is made and a record is taken of the beat before and after the application of a few drops of normal tap-water saline solution. The vago-sympathetic nerve is stimulated with a strong faradising current and the inhibition and after-effects (Fig. 45, Curve I.) are recorded. These tracings will serve as a control. The record is continued and several drops of a solution of cocaine, 1 part in 500 of normal tap-water saline solution, are allowed to flow over the heart. The beat will, in a few seconds, become irregular, and the ventricle will not beat to every contraction of the auricles (Fig. 45, Curve II.; Fig. 47). The heart-beat will become regular, but stimulation of the vago-sympathetic nerve will not produce inhibition (Fig. 46, Curve I.). Further doses will again produce irregular contractions with groups of beats (Fig. 46, Curve II.). The ventricular contraction is especially irregular in

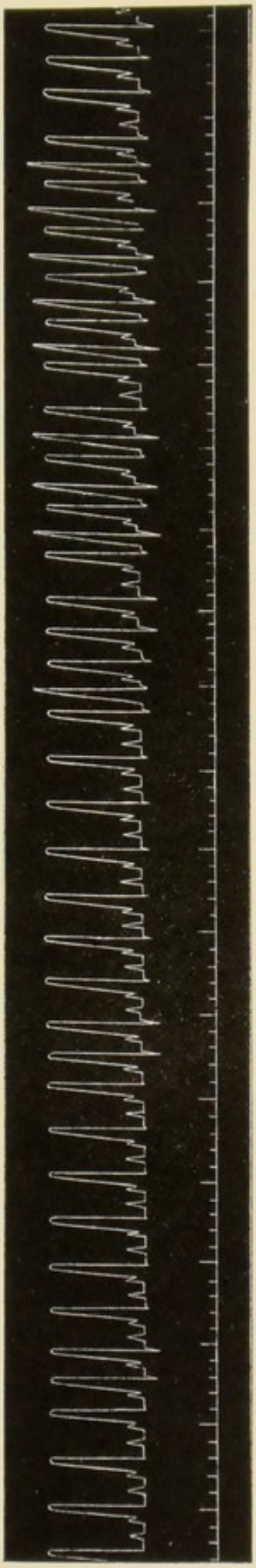


Fig. 47.—Contraction of the heart of a frog. The effect of cocaine, 1 part in 100 parts of normal tap-water saline solution. In the first portion of the tracing there are two contractions of the auricles to one of the ventricle; later, when the ventricular beat occurs, it is higher. The time is marked in seconds.

its appearance, and by further doses is abolished; the sinus and auricles still continue to beat feebly for some time after the cessation of the ventricular contraction (Fig. 46, Curve III.). A few drops of a stronger solution of cocaine may, if applied in the first instance, quickly stop all contraction of the heart.

EXPERIMENT LXI.—*The Effect upon the Nervous System.*—The previous experiments show that cocaine in small doses produces for a very short time an increase in the excitability of the central nervous system; this is followed by great depression and paralysis. Cocaine paralyses the vagus nerve and also acts in a similar manner upon the terminations of motor and sensory nerves. To show the last effect the toes of one foot of a frog are painted with a 1 per cent. solution of cocaine hydrochlorate. In a few minutes local anæsthesia is produced and pinching the toes no longer causes a reflex.

EXPERIMENT LXII.—*The Effect upon Muscle and Nerve.*[1]—Two muscle and nerve preparations are made, and their excitability is tested by a determination of the minimal stimuli. The nerve of the one (A) and the muscle of the other (B) are placed in a solution containing 1 part of cocaine hydrochlorate in 100 parts of normal tap-water saline solution; the muscle of the preparation A and the nerve of B are kept outside the watch-glass containing the drug. The excitability is again determined, and within a few minutes there will be no response to the stimulation of the nerve (B), but the muscle (B) will contract on direct stimulation. The terminations of the nerve (B) have been paralysed, for there is a good response of the muscle (A) to stimulation of its nerve. Soon the muscle (B) will not contract on direct stimulation and a decrease will be observed in the excitability of the nerve (A). Cocaine destroys the

[1] *The Effect upon the Eye.*—A few drops of a 1 per cent. solution of the drug are placed between the eyelids of a rabbit; local anæsthesia and dilatation of the pupil are produced. The reflex for light is, however, present. In weak doses the drug is said to stimulate the terminations of the dilator fibres from the sympathetic, and in large doses to depress the constrictor fibres of the motor oculi.

vitality of most forms of protoplasm, but acts most readily upon the terminations of nerves.

Pilocarpine

Pilocarpine nitrate, $C_{11}H_{16}N_2O_2 \cdot HNO_3$, is the nitrate of an alkaloid obtained from Jaborandi, *Pilocarpus pinnatifolius*. It is a white crystalline powder, soluble in 9 parts of water.

Experiment LXIII.—*The Effects of Poisonous Doses.*—Into the dorsal lymph-sac of a brainless frog are injected 10 minims (0·592 c.c.) of a 10 per cent. solution of pilocarpine nitrate in normal tap-water saline solution. In about fifteen minutes considerable loss of tone and power in the hind legs will be observed; the paralysis will increase and will involve the whole body. If, however, the frog be placed in a plate filled with water and covered by a bell-jar, it will recover from the effects of the drug in about twenty-four hours.

A dose of 15 minims (0·888 c.c.) of a 10 per cent. solution will cause complete paralysis and death in about three-quarters of an hour. A post-mortem examination will show the ventricle firmly contracted, but the auricles engorged with venous blood.

Experiment LXIV.—*The Effect upon the Heart.*—In a pithed frog the vago-sympathetic nerve is dissected out and the heart is exposed and connected with the cardiograph. A record of the normal beat and of the effect of stimulation of the vago-sympathetic nerve with a strong faradising current is taken, and then a few drops of a 10 per cent. solution of pilocarpine nitrate in normal tap-water saline solution are placed on the heart. The first effect is a slower contraction, and strong stimulation of the vago-sympathetic nerve at this stage produces no standstill, but an acceleration of the heart's beat (Fig. 48, Curve I.). When the effect of the stimulation has passed off and the heart is beating slowly, the application of a few drops of a weak solution of atropine sulphate in normal tap-water saline will quickly restore the rapidity of the contraction (Fig. 48, Curve II.).

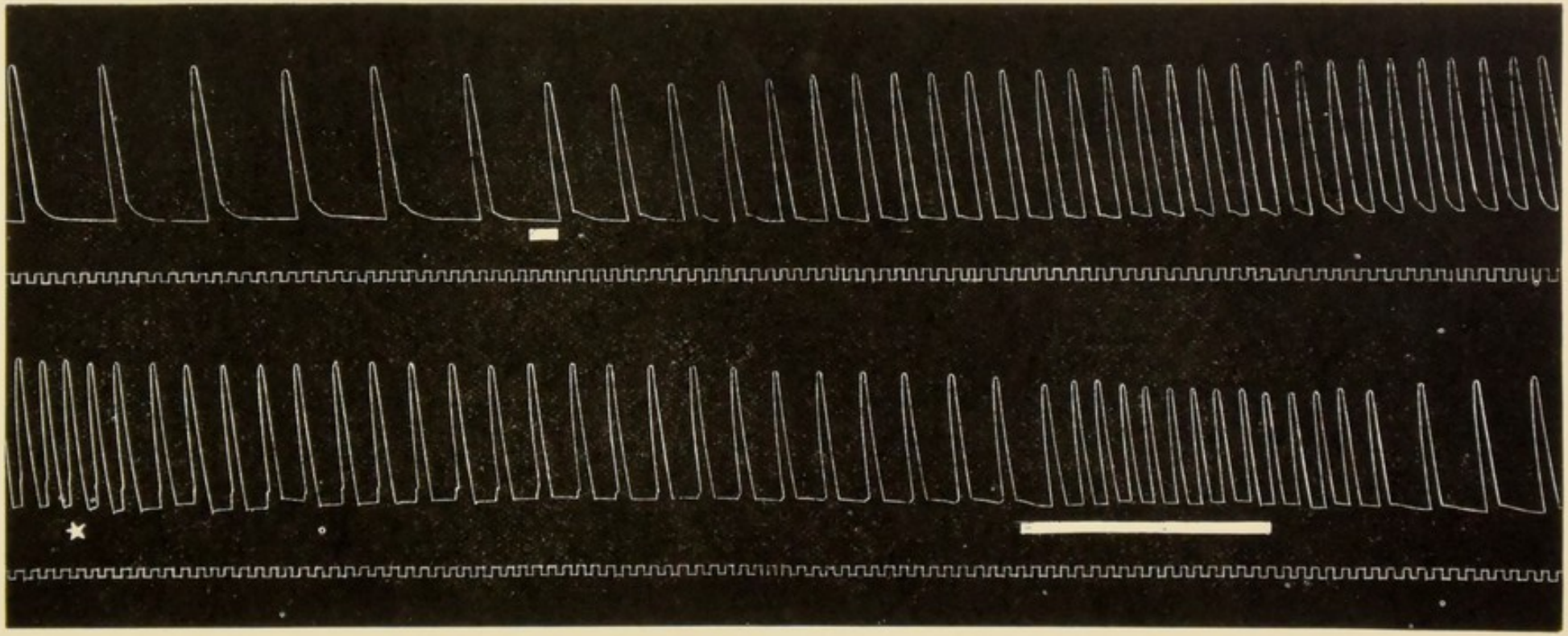


FIG. 48.—Contraction of a frog's heart. Curve I. The first three contractions are normal ones—before the application of two drops of a 10 per cent. solution of pilocarpine nitrate in normal tap-water saline at the point marked by the star. During the period marked by the horizontal line the vago-sympathetic nerve was stimulated by a strong faradising current of the same strength as that which previously stopped the heart. There is no standstill, but acceleration. Curve II. Continuation later of Curve I. At the point marked a weak solution of atropine sulphate in normal tap-water saline solution was applied. Temperature of air $= 17°$. Time marked in seconds.

The prolonged action of a 10 per cent. solution of pilocarpine nitrate causes a slow and irregular beat; the ventricle does not contract after each beat of the auricles (Fig. 49).

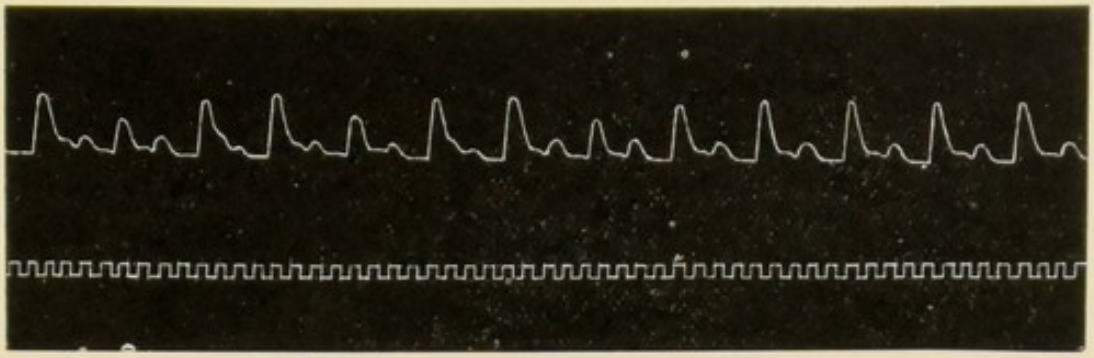


FIG. 49.—Contraction of a frog's heart. The later effects of a 10 per cent. solution of pilocarpine nitrate in normal tap-water saline. The ventricle does not respond to every contraction of the auricles. Temperature of air =14°. The time is marked in seconds.

Further doses will abolish the beat, but it can be restored by atropine.

The antagonism of atropine and pilocarpine is well marked. Atropine can restore the contraction of a heart which has

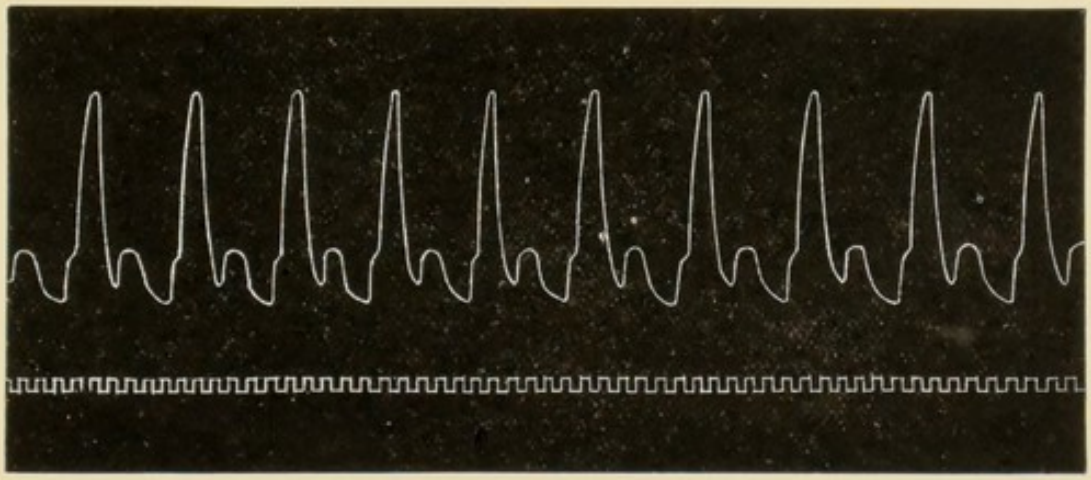


FIG. 50.—Contraction of a frog's heart. The typical effect of pilocarpine had been obtained, was removed by atropine, and then pilocarpine nitrate (10 per cent. solution in normal tap-water saline) was again applied. It caused a slower beat; the ventricle only responds to every second contraction of the auricles. Temperature of air =15°. The time is marked in seconds.

been poisoned with pilocarpine, and the latter drug can again stop the vigorous beat of an atropinised heart. This play upon the heart backwards and forwards can be repeated if the doses of the drugs are carefully adjusted.

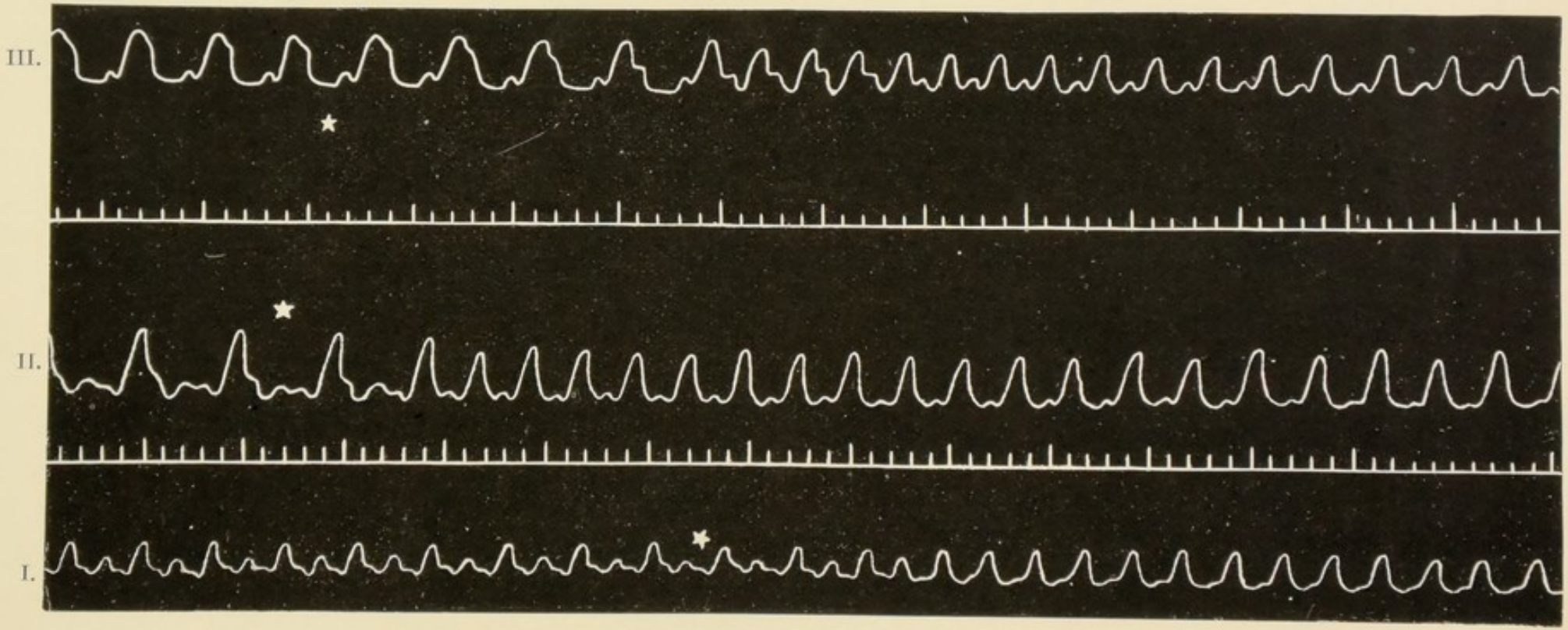


FIG. 51.—Contraction of the frog's heart. I. The heart was beating irregularly and was still irregular after the application of normal tap-water saline. At the point marked by the star two or three drops of a solution of pilocarpine nitrate (1 in 500) in normal tap-water saline were applied. II. Another heart to which similar remarks apply, except that the solution of pilocarpine nitrate was 1 in 1000. III. Another heart to which similar remarks to those for Curve II. apply. The contraction of the heart in each case becomes regular. The time is marked in seconds.

EXPERIMENT LXV.—*The Effect upon the Nervous System.*—The first experiment shows that pilocarpine causes paralysis by its action upon the central nervous system; the motor nerves are not affected by ordinary doses. The inhibitory action of the vagus nerve is abolished by pilocarpine.

EXPERIMENT LXVI.—*The Effect upon Muscle and Nerve.*[1]—Two muscle and nerve preparations are made, and their excitability is measured by the determination of the minimal stimuli. The muscle of one preparation and the nerve of the other are placed in a watch-glass filled with a 10 per cent. solution of pilocarpine nitrate in normal tap-water saline. Even after twenty minutes' exposure to the drug the nerve and muscle show little or no alteration in their excitability.

Muscarine

Muscarine (*Muscarinæ nitras*), $C_5H_{15}NO_3$, is an alkaloid prepared from a common fungus, Fly Agaric (*Agaricus muscarius*). It is a viscid, yellow liquid soluble in water.

Muscarine can be prepared artificially from cholin, $C_5H_{15}NO_2$, by oxidation with nitric acid, but this synthetic product differs somewhat in its physiological action from the natural alkaloid. In the mushroom cholin is found associated with muscarine.

EXPERIMENT LXVII.—*The Effect of Poisonous Doses.*—Into the dorsal lymph-sac of a brainless frog is injected 1 minim (0·059 c.c.) of a 10 per cent. solution of muscarine. Within a minute marked signs of poisoning will be observed. The hind legs will show convulsive twitches, and the front legs will be rigidly flexed over the sternum. The hind legs will then be flexed but are not rigid. A minute later all reflexes will be absent and the circulation of the blood in the web of the foot will have ceased.

[1] *The Effect upon the Eye.*—Local application of a solution of pilocarpine nitrate will cause marked contraction of the pupil of a rabbit's eye; the terminations of the motor oculi are stimulated. Atropine will remove the contraction and cause dilatation.

An examination of the body will show that the heart has ceased to beat and that the auricles and ventricle are distended with fluid venous blood. The muscles and nerves are readily excited by an electrical stimulus.

EXPERIMENT LXVIII.—*The Effect upon the Heart.*—A record is taken of the beat of a heart before and after the

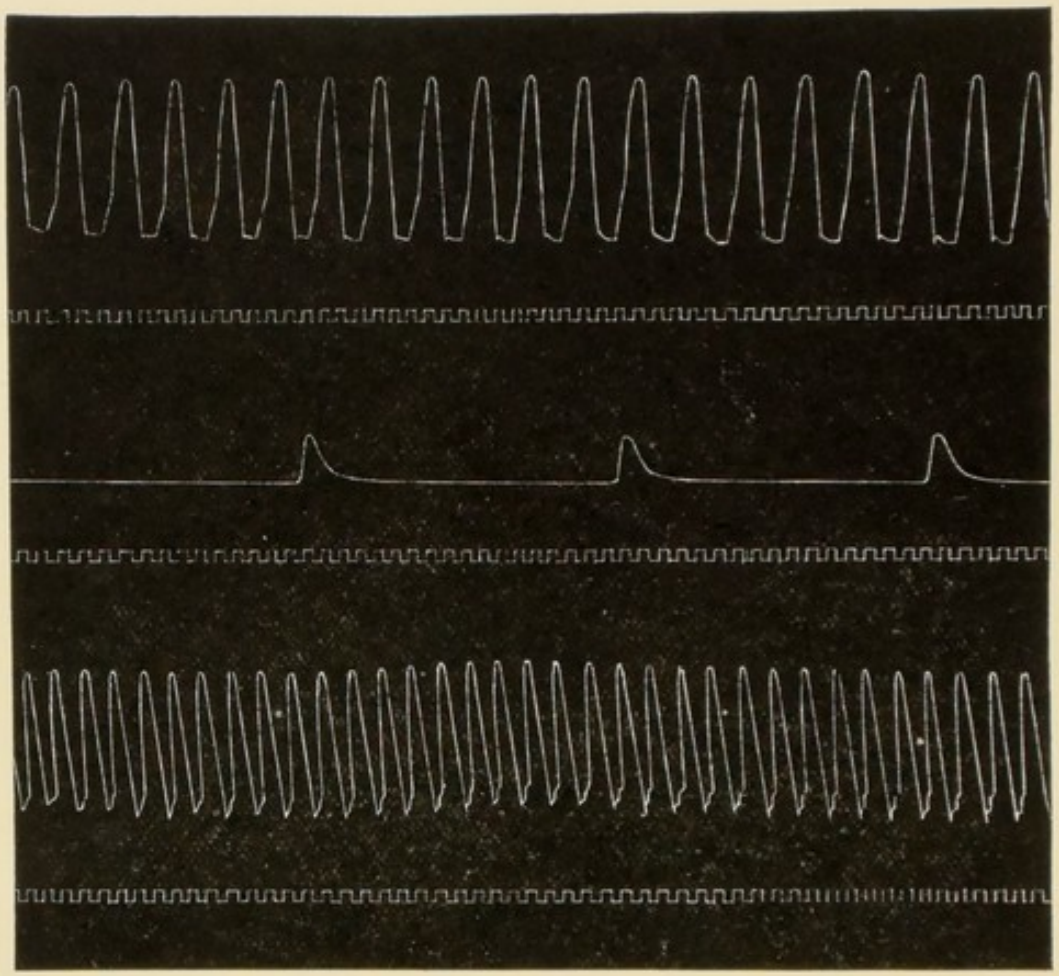


FIG. 52.—Contraction of a frog's heart. I. Normal. II. Three minutes after the application of one drop of a 10 per cent. solution of muscarine. III. Three minutes after the application of a weak solution of atropine sulphate in normal tap-water saline. It will be seen that the rhythmic contractions are restored and the contraction and relaxation become so complete that the excursion of the lever is greater than in Curve I., but the frequency is less. The time is marked in seconds.

application of a few drops of normal tap-water saline solution; one drop of a 10 per cent. solution of muscarine is then placed on the heart. The effect is seen almost immediately. The heart beats much more slowly and feebly (Fig. 52, Curve II.),

or it may cease to beat and remain in diastole for a minute or two (Fig. 53), and then beat slowly and feebly. A few drops of a weak solution (0·2 per cent.) of atropine sulphate are now placed on the heart; in a few seconds the heart begins to beat (Fig. 54, Curve II.), or, if it be still contracting, it beats more frequently and with greater force until the contractions become very forcible, and, owing to the complete relaxation of the heart, the excursion of the lever is greater than in the case of the normal beat at the commencement of the experiment (Fig. 52, Curve III.). The vigour of

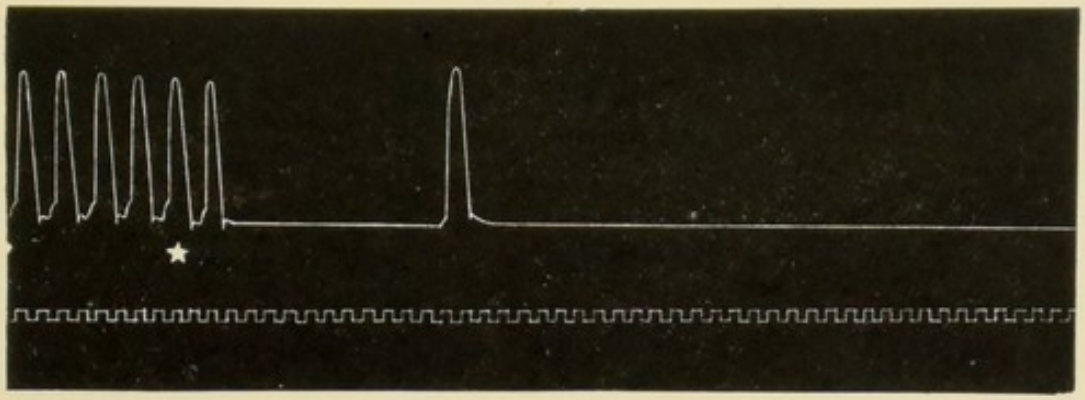


FIG. 53.—Contraction of a frog's heart. At the point indicated by the star two drops of a 10 per cent. solution of muscarine were applied. Two minutes after the end of this curve the heart commenced to contract again with a slow and feeble beat. The time is marked in seconds.

the contraction, especially of the ventricle, and the marked relaxation are readily observed by the eye alone.

After the application of atropine a further dose of muscarine will not readily bring about its characteristic effects, although there will be a slower and more feeble beat.

If, during the standstill produced by muscarine, the vago-sympathetic be stimulated by a strong faradising current, the heart begins to beat and shows a "staircase" of contractions. After the stimulation the contractions become smaller and soon cease (Fig. 54, Curve I.).

EXPERIMENT LXIX.—*The Effect upon the Nervous System.*—The first experiment upon the effect of muscarine shows that the drug at first stimulates, then depresses profoundly the excita-

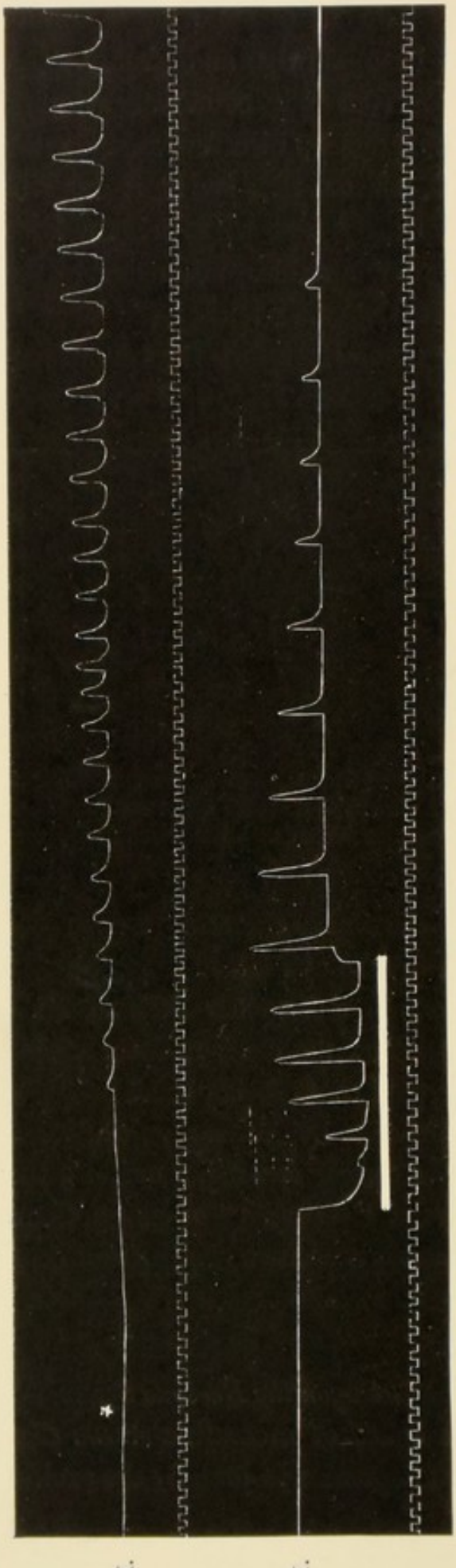


FIG. 54.—Contraction of a frog's heart. I. Standstill had been produced by muscarine, and then, during the period indicated by the white line, the vago-sympathetic nerve was stimulated by a strong faradising current. The fall in the base line was due to an escape of current, which stimulated the muscles of the floor of the mouth. II. Continuation of I. At the point indicated by the star a weak solution of atropine sulphate in normal tap-water saline was applied. The time is marked in seconds.

bility of the central nervous system and causes death. The nerves are still excitable after the death of the frog.

EXPERIMENT LXX.—*The Effect upon Muscle and Nerve.*[1] — Two muscle and nerve preparations are made, and their excitability is determined. The muscle of the one (A) is placed in a 5 per cent. solution of muscarine in normal tap-water saline; its nerve is kept outside on moist filter-paper. The nerve of the other preparation (B) is placed in the solution of the drug, and its muscle is laid upon the filter-paper. After about ten minutes the excitability of the preparations is

[1] *The Effect upon the Eye.*—In this respect muscarine resembles pilocarpine. See p. 75.

again determined; there is little change; the muscle exposed to the drug is somewhat less excitable.

Veratrine

Veratrine, $C_{32}H_{49}NO_9$, is an alkaloid obtained from Veratrum sabadilla (*Schœnocaulon officinale*), cevadilla and Veratrum viride (green hellebore). It is a white amorphous powder, odourless but irritating to the nostrils, very bitter and acrid to the taste. It is almost insoluble in water (1 in 1000), but is soluble in dilute acids.

Experiment LXXI.—*The Effects of Poisonous Doses.*—Under the skin of a brainless frog are injected 5 minims (0·296 c.c.) of a saturated solution (1 in 1000) of veratrine in normal tap-water saline solution. In about ten minutes it will be observed that the hind legs are very slowly and imperfectly flexed after a jump, and a few minutes later the frog will be seized by a spasm when it jumps; the hind legs are rapidly stretched out behind and the front legs are extended along the flanks, so that the frog is pitched on its nose. The hind legs are drawn up slowly, and a quivering movement of the muscles of the thigh are seen. The frog cannot readily relax its muscles. After the spasm the frog assumes a more or less normal attitude. These spasms are repeated every few minutes, after each jump; but one spasm cannot be immediately evoked after another. In about a quarter of an hour after the injection a marked loss of reflex power is observed, but this gradually passes off and the reflexes from the cornea and skin return. An increased secretion of mucus from the skin is observed. If the frog be kept in shallow water and covered with a bell-jar, it will in a few hours completely recover from the poisonous effects of the drug.

A dose of 15 minims (0·888 c.c.) of a saturated solution (1 in 1000) is fatal to a frog. The heart is stopped in the systolic phase.

Experiment LXXII.—*The Effect upon Muscle and Nerve.*—

(*a*) A brainless frog is poisoned with 5 minims of a saturated solution (1 in 1000) of veratrine in normal tap-water saline. As soon as the characteristic delay in the recovery of the hind legs after a jump is observed, the remaining portions of the central nervous system are destroyed and a preparation is made of the sciatic nerve and the gastrocnemius muscle. The muscle is connected with a myograph. Stimulation by a single induction shock produces a smart initial twitch followed by a prolonged contraction (Fig. 55), but if the muscle is repeatedly stimulated the type of contraction is altered to a single twitch (Fig. 55).

FIG. 55.—Contraction of the gastrocnemius muscle of a frog. The effect of veratrine. The first two contractions show the characteristic effect of the drug; further stimulation produced twitches without the prolonged contraction. The time is marked in seconds. The curve has been reduced to one-half the actual size. The time is marked in seconds.

(*β*) The effect of veratrine upon muscle can also be shown in the following way. A frog is pithed, and then the lower jaw is completely removed so far back as to include the hyoid bone; care is taken to avoid injury to the tongue. The free extremity of the tongue is connected by means of a small bent pin with a thread attached to the lever of a myograph; the origin of the hyoglossus muscle is fixed by a pin passing through the hyoid bone into the cork of the myograph. The fibres of the hyoglossus muscle in the tongue are stimulated by an induction current, and the contraction is recorded. Two or three drops of a saturated solution (1 in 1000) of veratrine are injected under the mucous membrane of the tongue, and then records of the contraction of the muscle are taken. The muscle will respond with the prolonged contraction characteristic of muscle poisoned by veratrine; if the stimulation be repeated frequently the effect will pass off, but will reappear after an interval of rest.

(γ) Two muscle and nerve preparations are made, and their excitability is tested by a determination of the minimal stimuli. The muscle of the one preparation (A) is placed in a watch-glass filled with a saturated solution (1 in 1000) of veratrine in normal tap-water saline; the nerve is kept outside; the nerve of the other preparation (B) is placed in the solution of the drug, but its muscle is laid outside. Within a few minutes there will be a marked decrease in the response of the muscle (A) to stimulation of its nerve, and the application of the electrodes directly to the muscle will show some loss of excitability. Later stimulation of the nerve (A) with the strongest current will cause no contraction, and the muscle will give only a quivering contraction when it is stimulated with a similar current. The nerve and muscle of preparation B will show but very slight loss in excitability.

Veratrine has, therefore, little or no effect upon the trunk of the nerve, but acts upon the terminations of the nerves in the muscle and especially upon the muscular tissue itself. Waller has shown that protoveratrine, $C_{32}H_{51}NO_{11}$, differs markedly in its physiological action from veratrine, $C_{32}H_{49}NO_9$; it acts upon the nerve and not upon the muscle.

Experiment LXXIII.—*The Effect upon the Heart.*—The vago-sympathetic nerve of a pithed frog is dissected out, and the heart is connected with a cardiograph. A record is taken of the normal beat, and of the inhibition produced by stimulation of the vago-sympathetic nerve with a strong faradising current. A few drops of a saturated solution (1 in 1000) of veratrine in normal tap-water saline are allowed to flow from a small pipette over the heart. The contractions of the heart soon become slower and more prolonged; this is especially seen in the ventricle (Fig. 56, Curves II. and III.). Stimulation of the vago-sympathetic nerve will not produce inhibition (Fig. 56, Curve II.). A further dose of the drug may increase the contraction of the ventricle so much that it does not relax before the next auricular contraction appears; thus the ven-

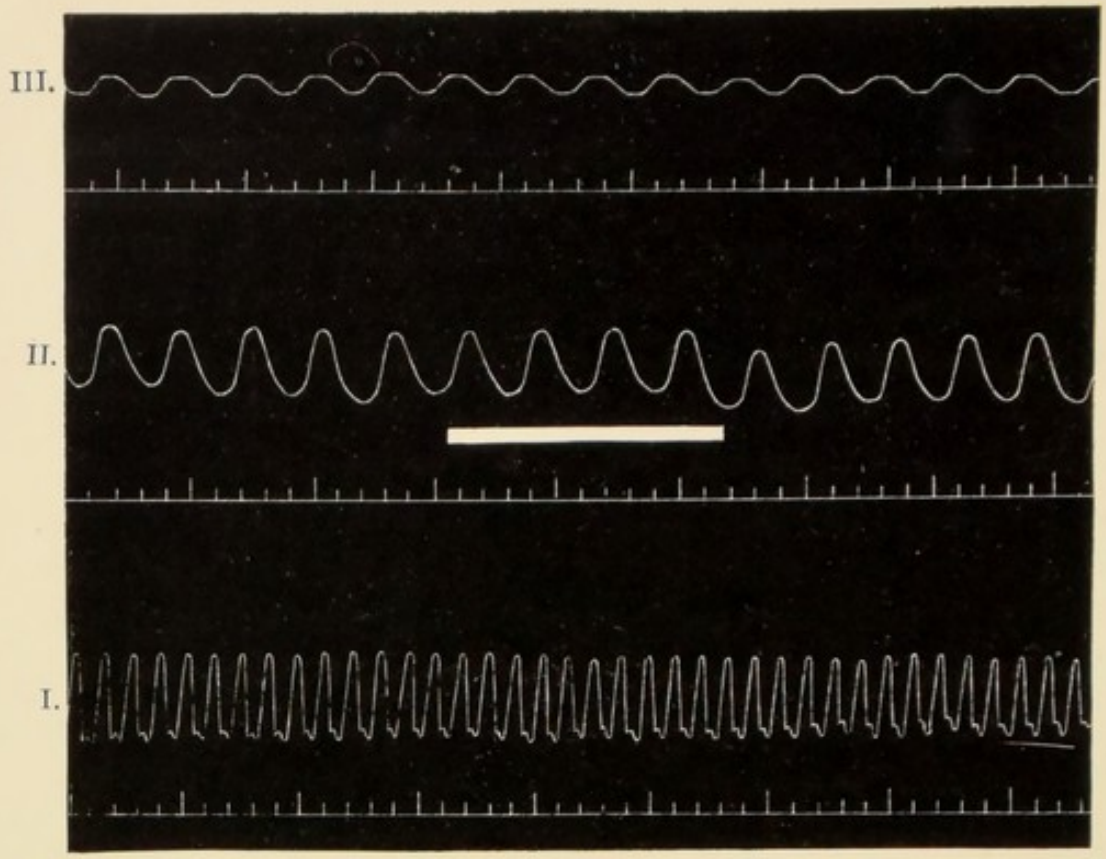


FIG. 56.—Contraction of a frog's heart. I. Normal. II. Effect of a saturated solution of veratrine (1 in 1000) in normal tap-water saline. Stimulation of the vago-sympathetic nerve with a strong faradising current does not stop the beat. III. Later effect. Temperature of air = 19°. The time is marked in seconds.

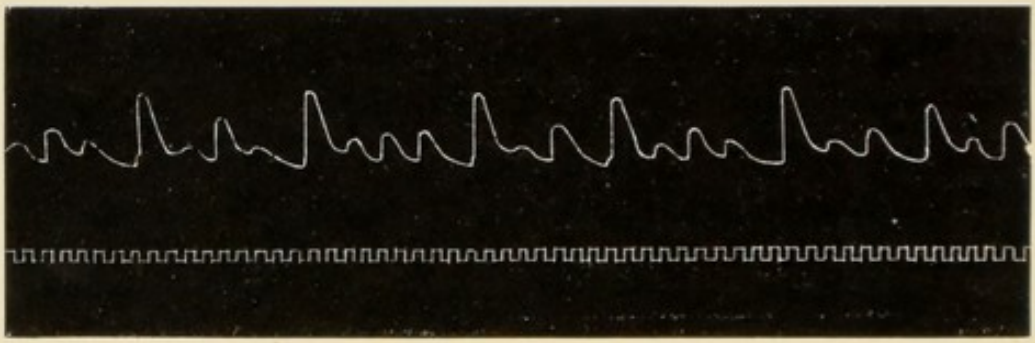


FIG. 57.—Contraction of a frog's heart. The effect of continued application of a saturated solution (1 in 1000) of veratrine in normal tap-water saline. The ventricle is entering into a partly contracted condition, and does not respond, or responds incompletely, to each auricular contraction. Temperature of air = 16°. The time is marked in seconds.

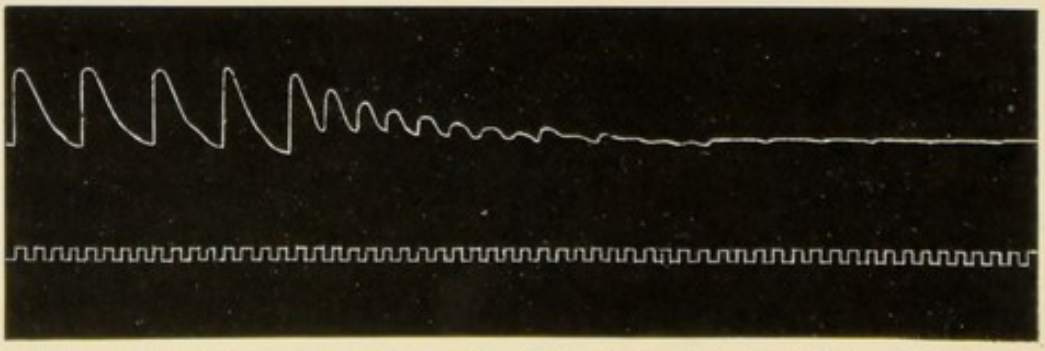


FIG. 58.—Contraction of a frog's heart. The effect of continued application of a saturated solution (1 in 1000) of veratrine in normal tap-water saline. Temperature of air = 12°. The time is marked in seconds.

tricle is unable to respond to each auricular beat (Fig. 57). A portion of the ventricle may remain permanently contracted, and by further doses the entire ventricle can be made to pass into a contracted condition (Fig. 58); it is killed in the systolic stage.

EXPERIMENT LXXIV.—*The Effect upon the Nervous System.*—The previous experiments have shown that veratrine at first stimulates and then paralyses the central nervous system.

Digitaline

Digitaline, $C_{50}H_{40}O_{30}$, is a glucoside prepared from the leaves of *Digitalis purpurea*, purple foxglove. The "digitaline" of commerce varies considerably in its composition, and often contains digitoxin, digitophyllin, and digitonin, as well as digitaline. According to Kiliani, digitonin and digitin are identical with digitalinum crystallisatum (Merck), which in the pure state is said to be physiologically inactive. Digitalinum crystallisatum is almost insoluble in water, but we have found that a saturated solution of this preparation in normal tap-water saline possesses well-marked action upon the heart of the frog.

The pure German digitaline (Digitalin. pur. pulv. Germanic, Merck) consists of the glucosides digitin, digitalein (Schmiedeberg), and digitalinum verum (Kiliani). It is a yellowish-white powder, and its solubility is about 1 part in 3 parts of water.

EXPERIMENT LXXV.—*The Effect of Poisonous Doses.*—Into the dorsal lymph-sac of a brainless frog are injected 11 minims (0·651 c.c.) of a 2 per cent. solution of digitaline (Merck's Digitalin. pûr. pulv. Germanic) in normal tap-water saline. In a few minutes there will be a considerable decrease in the excitability of the nervous system, and in about half an hour there will be complete paralysis, followed by death. An examination of the body will show that the ventricle of

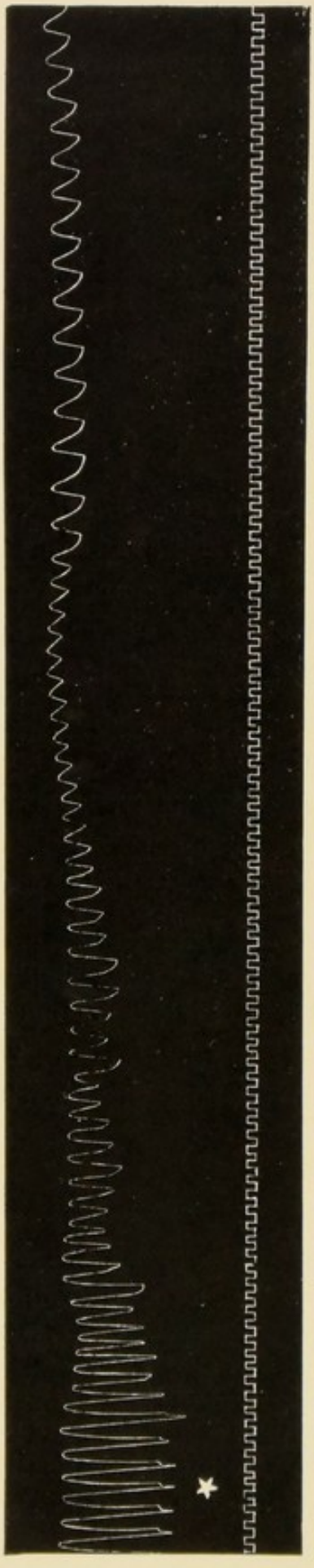


Fig. 59.—Contraction of a frog's heart. The first three or four contractions are normal—before the application at the point marked by the star of two or three drops of a 2 per cent. solution of soluble digitaline (Digitalin. pur. pulv. Germanic, Merck) in normal tap-water saline. Temperature of air = 15°. The time-mark in seconds serves as a base-line.

the heart is pale and contracted, but the auricles are distended with venous blood. The muscles and nerve retain their excitability for some time after the death of the animal.

Smaller doses, 5 minims (0·296 c.c.), of a 1 per cent. solution will produce death after an interval of several hours. The drug possesses an irritant action upon the tissues at the seat of injection, and here causes a darkening and separation of the external layer of the epidermis of the skin.

Death was caused by 30 minims (1·776 c.c.) of a saturated solution of crystalline digitaline (Merck), but half that dose produced no symptoms of poisoning in a brainless frog.

Experiment LXXVI.—*The Effect upon the Heart.*—A record is taken of the contraction of the heart of a pithed frog before and after the application of normal tap-water saline solution, and after stimulation of the vago-sympathetic nerve with a strong faradising current. This portion of the tracing will serve as a control. Two or three drops of a 2 per cent. solution of digitaline (Digitalin.

pur. pulv. Germanic) are now applied to the heart. The effect is seen almost immediately. The ventricle contracts vigorously,

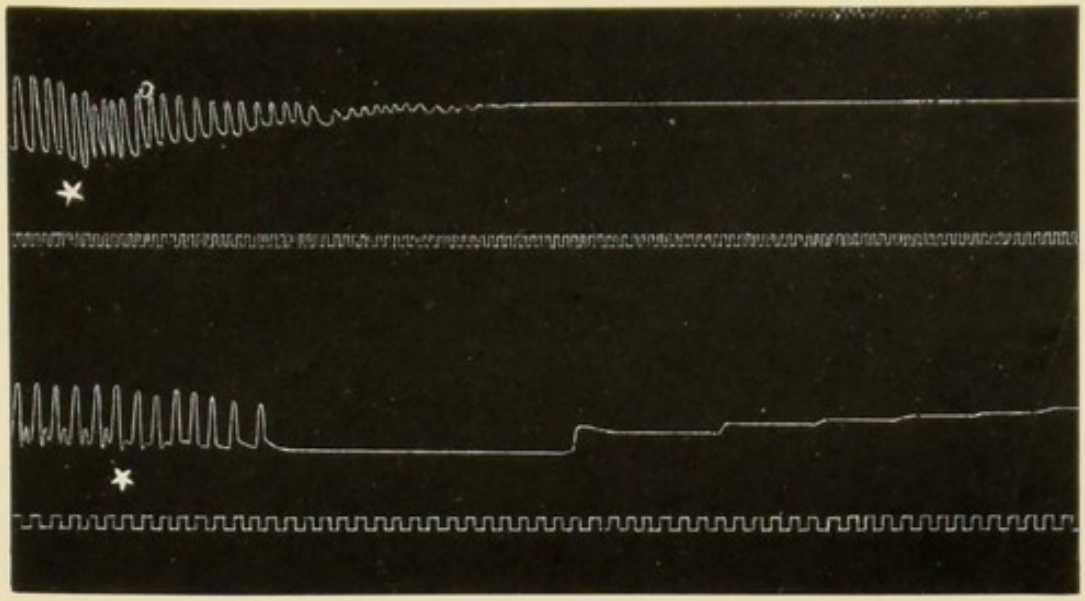


FIG. 60.—Curve I. The first three or four contractions are normal—before the application at the point marked by the star of two or three drops of a 1 per cent. solution of soluble digitaline (Digitalin. pur. pulv. Germanic, Merck). Curve II. Another heart. The first three or four contractions are normal. At the point marked by the star two or three drops of a 2 per cent. solution of soluble digitaline were applied. Temperature of air = 19°. The time is marked in seconds.

but relaxes only slightly during diastole; the tone of the cardiac muscle is greatly increased, as shown by the increased height

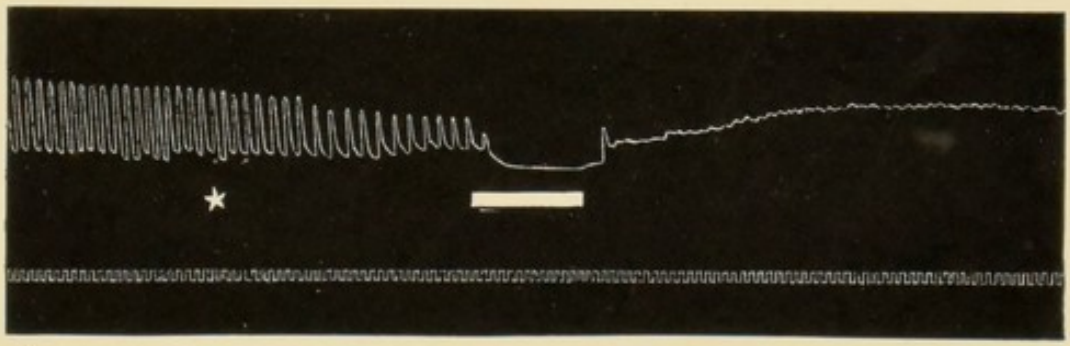


FIG. 61.—Contraction of a frog's heart. At the point marked by the star a further dose of a 0·5 per cent. solution of soluble digitaline was applied. The vago-sympathetic was stimulated by a strong faradising current during the period marked by the horizontal line. Temperature of air = 19°. The time is marked in seconds.

of the curve above the base-line, and the beats are slower (Fig. 59). Further application of the drug will stop the contraction of the ventricle in the systolic phase, but the

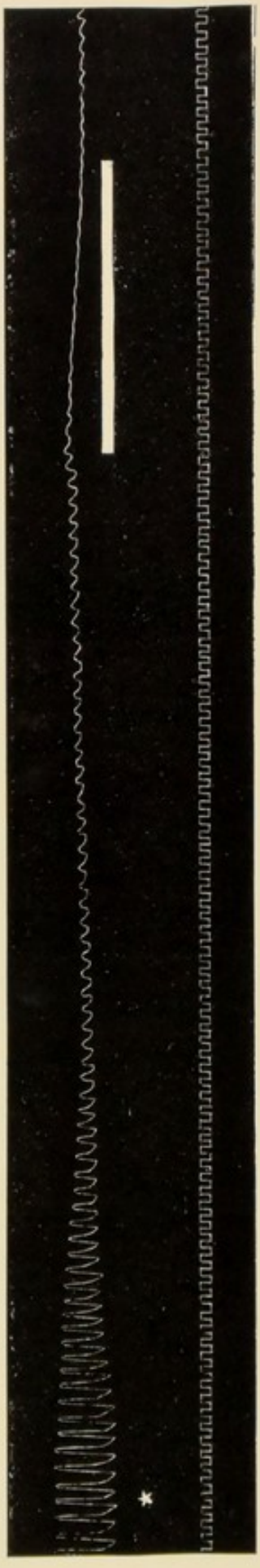


Fig. 62.—Contraction of a frog's heart. The first two or three contractions are normal, then at the point marked by the star two or three drops of a 0·5 per cent. solution of soluble digitaline in normal tap-water saline were applied. During the period marked by the horizontal line the vago-sympathetic nerve was stimulated with a strong faradising current. Temperature of air = 19°. The time is marked in seconds.

auricles and sinus will continue to beat (Fig. 63, Curve II.).

A larger dose will cause the heart to pass into a firmly contracted condition, and it is killed in the systolic phase (Fig. 60, Curve II.). Sometimes the heart at first ceases to beat in the diastolic phase, and a few seconds later passes by a series of slow contractions into the rigid systolic condition (Fig. 60, Curve I.).

During the first stage of the action of digitaline strong stimulation of the vago-sympathetic nerve will cause standstill and relaxation (Fig. 61), but in the later stages the effect is less marked (Fig. 62).

The almost insoluble crystalline digitaline (Merck) will produce the characteristic effects of digitaline; a saturated solution in normal tap-water saline should be used.

Experiment LXXVII.—*The Effect upon the Nervous System.* — The experiment upon the effect of poisonous doses of digitaline showed

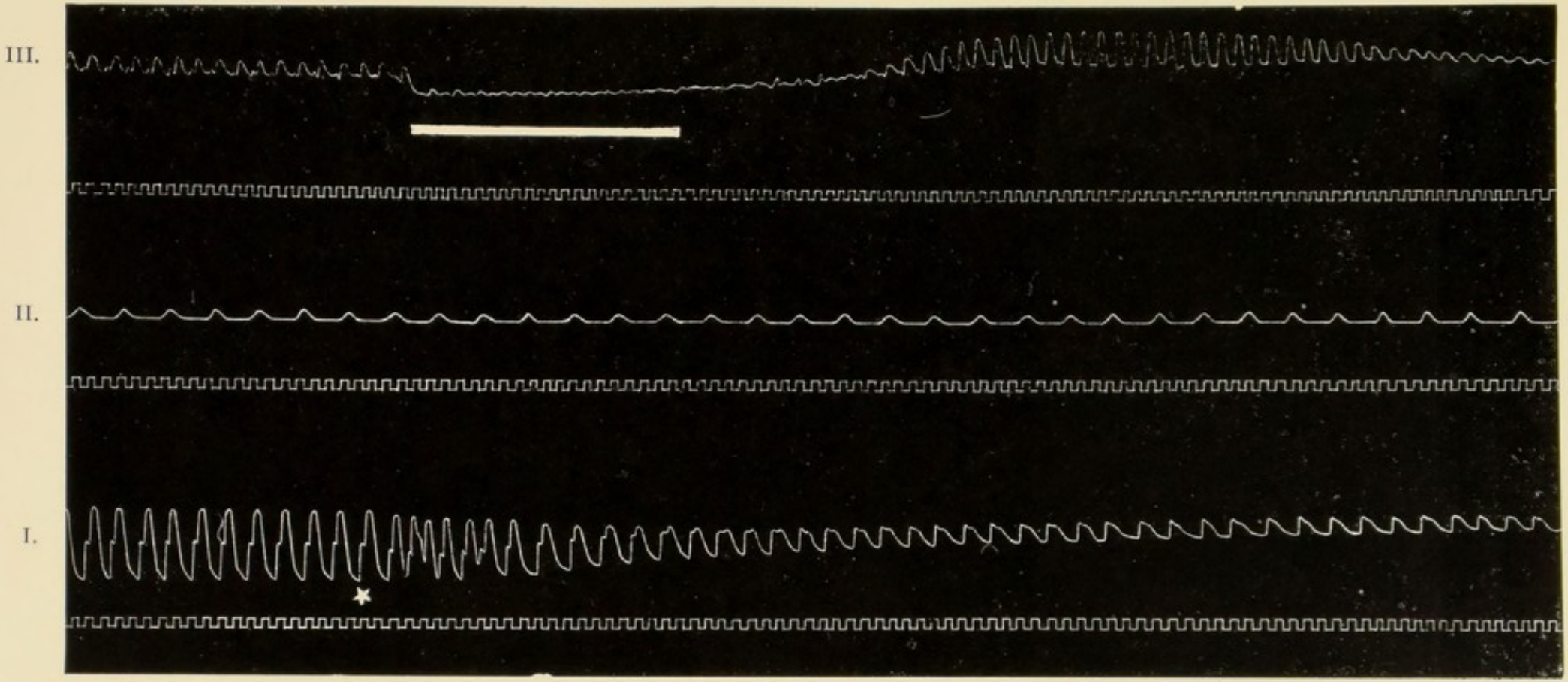


FIG. 63.—Curve I. Contraction of a frog's heart. At the point marked by the star 3 minims of a saturated solution of crystalline digitaline (Merck) in normal tap-water saline were poured from a pipette over the heart. Curve II. Continuation of Curve I. Only the sinus and auricles are beating. The ventricle is firmly contracted. Temperature of air = 18·5°. Curve III. From another heart. The effect of strong stimulation of the vago-sympathetic nerve upon the contraction of a heart under the influence of a saturated solution of crystalline digitaline (Merck). Temperature of air = 19°. The time is marked in seconds.

that the drug paralyses the central nervous system. The

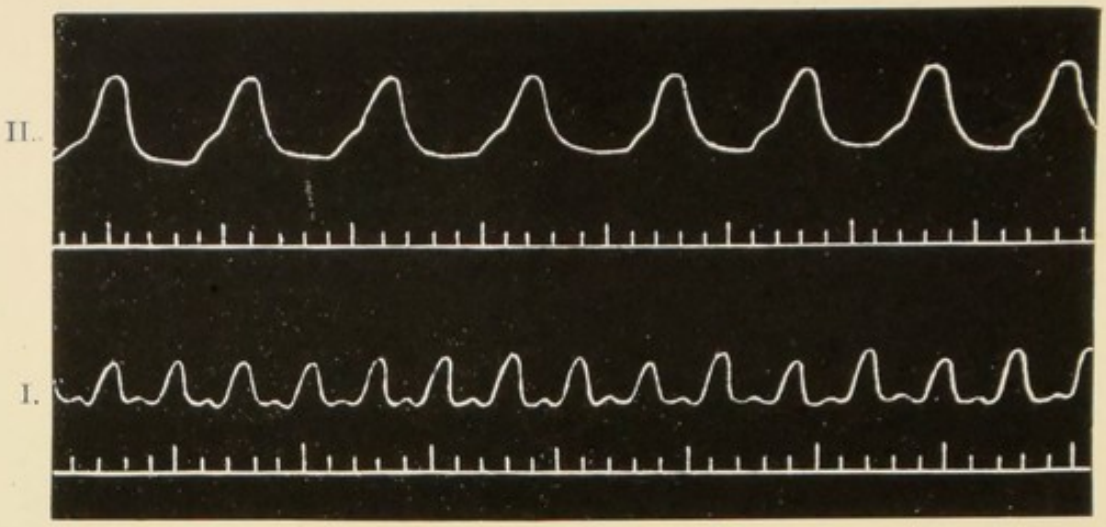


FIG. 64.—Contraction of a frog's heart. Curve I. Normal tap-water saline alone had been applied. Curve II. A few drops of a saturated solution of crystalline digitaline (Merck) had been applied. The time is marked in seconds.

nerves and muscles are still excitable after the death of the animal.

EXPERIMENT LXXVIII.—*The Effect upon Muscle and Nerve.* —Two muscle and nerve preparations are made, and their excitability is determined by observations of the minimal stimuli. The muscle of one (A) is placed in a 0·5 per cent. solution of digitaline (Digitalin. pur. pulv. Germanic, Merck) in normal tap-water saline; the nerve is placed outside the watch-glass containing the drug. The nerve of the other preparation (B) is placed in the solution of the drug, and its muscle is kept outside on filter-paper moistened with normal tap-water saline solution. The muscle (A) quickly shortens, and shows a great decrease in its excitability when stimulated directly and indirectly; the nerve (B) shows no change.

Similar results are obtained with a saturated solution of crystalline digitaline (Merck).

Digitaline has a marked action upon muscle, but in ordinary doses does not affect the nerve-trunks.

Physostigmine

Physostigmine, or *Eserine*, $C_{15}H_{21}N_3O_2$, is an alkaloid obtained from the Calabar bean or Ordeal bean (*Physostigma venenosum*). It grows in West Africa, and was formerly used by the natives in trials by ordeal. The sulphate of physostigmine is a colourless or faintly pink crystalline substance soluble in water; the solution, at first colourless, soon becomes red.

Experiment LXXIX.—*The Effects of Poisonous Doses.*—Under the skin of a brainless frog is injected a dose of 20 minims (1·184 c.c.) of a 1 per cent. solution of physostigmine[1] in normal tap-water saline. In about fifteen minutes the frog will show marked loss of tone and will lie with its limbs outstretched; reflexes are still present, but they are sluggish; respiration soon ceases; the reflexes disappear and death occurs in an hour or two after the administration of the poison.

The effects of smaller doses, 10 minims (0·592 c.c.), are slight, and the frog will recover if it be kept moist under a bell-jar.

Experiment LXXX.—*The Effect upon the Heart.*—The vago-sympathetic nerve is dissected in a pithed frog, and the heart is connected with the lever of a cardiograph. A record of the heart's beat before and after the application of a few drops of normal tap-water saline solution is taken as a control. The record is continued and the vago-sympathetic nerve is stimulated by a strong faradising current; the heart-beat is inhibited. A few drops of a 1 per cent. solution of physostigmine in normal tap-water saline solution are applied. The heart-beat becomes slower and the relaxation is less complete owing to the increased tone of the cardiac muscle (Fig. 65, Curve I.). A further dose will cause a much slower

[1] Physostigmine sulphate.

beat, and one apparently more powerful (Fig. 65, Curve II.); this is due to loss of the abnormal tone of the muscle; the

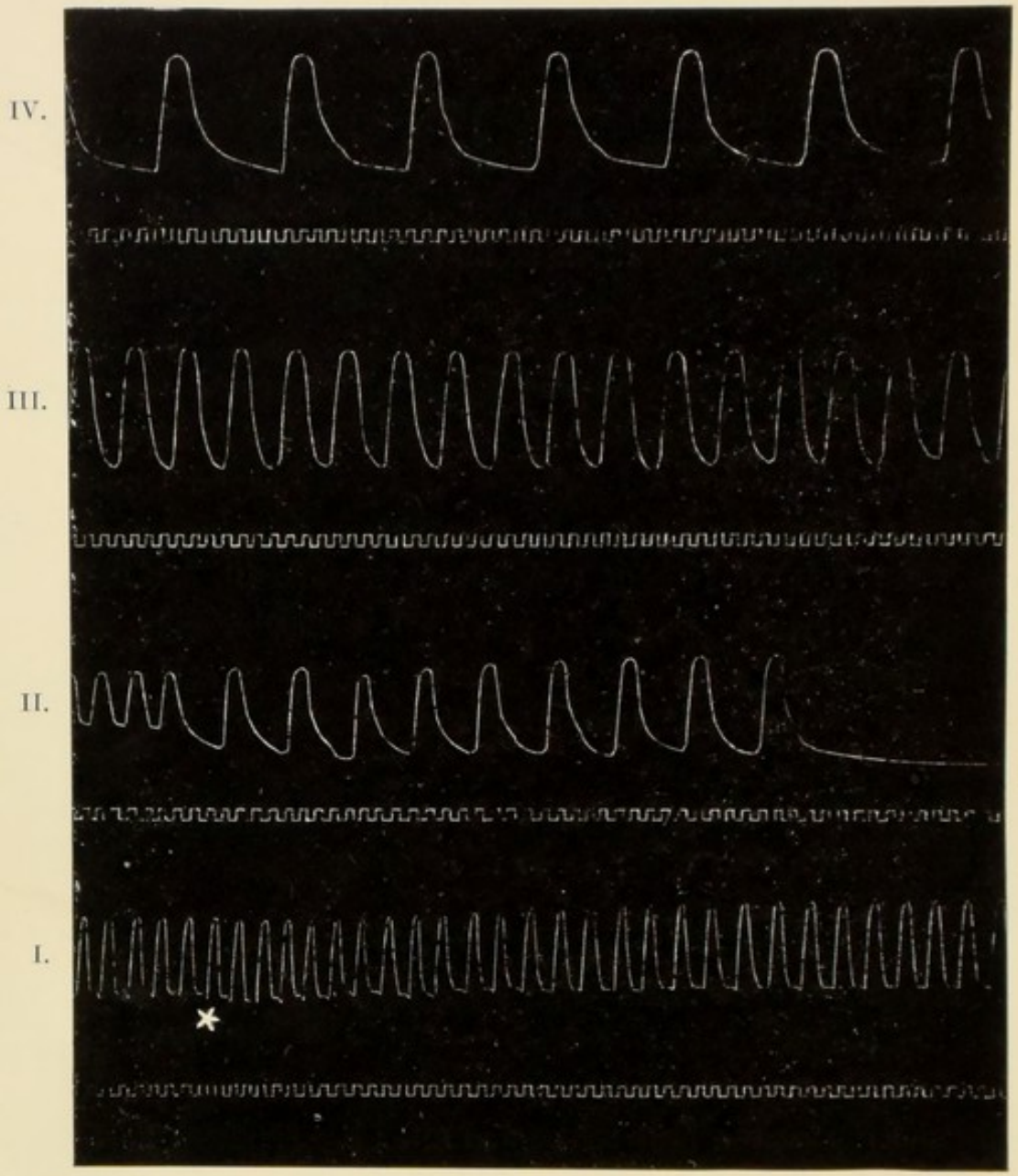


FIG. 65.—Contraction of a frog's heart. I. The first five contractions are normal—before the application at the point marked by the star of two or three drops of a 1 per cent. solution of physostigmine in normal tap-water saline. II. The effect of a further dose of the drug. The heart ceased to beat for about one minute. III. The beat was restored by a drop or two of a 1 per cent. solution of atropine sulphate. IV. The effect of another dose of physostigmine. Temperature of air = 18·5°. The time is marked in seconds.

relaxation is much more complete and the heart may cease to beat in the diastolic phase. The contraction, however, can be restored by a drop or two of a 1 per cent. solution of atropine

sulphate in normal tap-water saline (Fig. 65, Curve III.). The beats then become more rapid, but not so frequent as in the normal; they are more powerful owing to the more complete relaxation. Another dose of physostigmine will cause a slower beat and the phase of relaxation will be prolonged (Fig. 65, Curve IV.). There is, therefore, as Fraser and others have shown, an antagonism between atropine and physostigmine.

Stimulation of the vago-sympathetic nerve in the very early stages of the action of physostigmine will cause standstill of the heart, but in the later stages it produces only a slight slowing of the heart or no effect.

Experiment LXXXI.—*The Effect upon the Nervous System.*—The first experiment upon the action of physostigmine shows that the drug at first depresses and then paralyses the central nervous system of the frog. The nerves are still excitable after the death of the animal.

Experiment LXXXII.—*The Effect upon Muscle and Nerve.*—Two muscle and nerve preparations are made, and their excitability is determined. The muscle of the one and the nerve of the other are placed in a watch-glass full of a 1 per cent. solution of physostigmine in normal tap-water saline solution. After an interval of about fifteen minutes the excitability is again tested, but little change can be observed.

Upon the eye physostigmine has a marked effect. This can be easily shown by placing a drop or two of a 1 per cent. solution of the drug between the eyelids of a rabbit. The pupil is soon greatly contracted. The terminations of the motor oculi are said to be stimulated. A drop or two of a weak solution of atropine will antagonise the action of the physostigmine and will cause dilatation. A further dose of physostigmine will in turn diminish the dilatation produced by the atropine.

Suprarenal Gland

The Suprarenal Gland is a ductless gland which produces an internal secretion. The work of G. Oliver and Schäfer has shown that an extract of the medulla of the gland contains an active principle which produces striking physiological effects; it increases the tone of all muscular tissue.

In the following experiments upon the frog an extract of the medulla of the suprarenal gland in normal tap-water saline solution should be used.

Experiment LXXXIII.—*The Effect of Poisonous Doses.*—Under the skin of the back of a brainless frog is injected a dose of the extract equivalent to 0·3 gramme of the fresh gland. In about fifteen minutes the movements of the frog become sluggish, but the reflexes are present. The depression increases and the animal becomes partly paralysed, and is unable to recover itself if it be placed on its back. The effects of the extract disappear in about half an hour.

Recovery will occur even from much larger doses.

Experiment LXXXIV.—*The Effect upon the Heart.*—A record of the contraction of the heart of a pithed frog

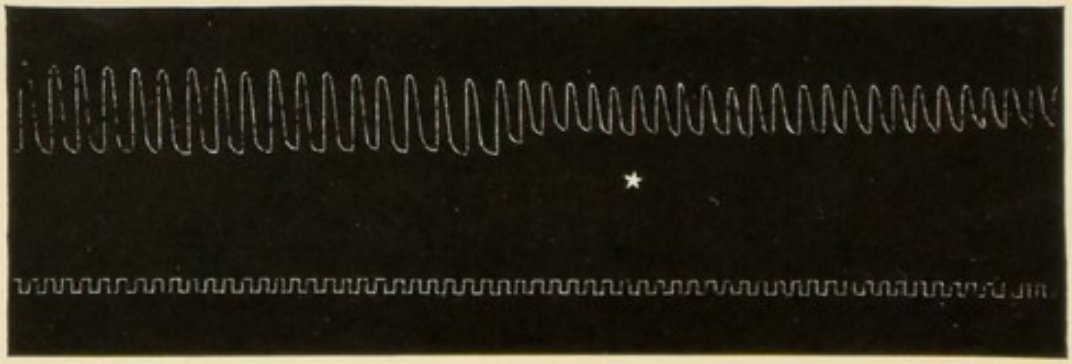


Fig. 66.—Contraction of a frog's heart. At the point indicated by the star a few drops of suprarenal extract were applied. The time is marked in seconds. The temperature of the air was 18°.

is taken before and after the application of a few drops of normal tap-water saline solution. The record is continued and a few drops of an extract of suprarenal gland in normal

tap-water saline solution are allowed to flow over the heart; the tone of the muscle is increased and the relaxation is thus less complete (Fig. 66). Sometimes the heart at first beats more slowly and then more quickly and with increased tone. Stimulation of the vago-sympathetic nerve with a strong faradising current will still produce inhibition.

Experiment LXXXV.—*The Effect upon the Blood-Vessels.*—In a pithed frog the mesentery is exposed and placed under the low power of a microscope; the diameter of a blood-vessel is determined by a micrometer-scale, and then a drop of suprarenal extract in normal tap-water saline is placed over the vessel. A contraction of the muscle-fibres of the vessel quickly occurs and the diameter of the blood-vessel may be reduced by about one-third.

The extract of suprarenal gland has been successfully used in medicine to prevent hæmorrhage from small blood-vessels.

The effect of the extract upon the blood-vessels can also be shown by the following experiment. A small glass cannula is connected by a piece of rubber-tubing and a bent glass tube with a small beaker, and, after the whole apparatus has been filled with normal tap-water saline solution, a clip is placed upon the tubing. The brain of a frog is destroyed and the heart is exposed; a ligature is passed round the left aorta, and through a cut in the ventricle the cannula is passed and tied into the aorta. An opening is made into the sinus venosus. The frog is suspended by its jaw; the beaker is raised above the head of the frog; the clip is removed and the fluid passes into the aorta through the arteries, capillaries, and veins, and escapes from the cut in the sinus venosus. It drips off the toes of the frog. The number of drops in a given time is counted, and, when the flow is constant, some extract of suprarenal gland is placed in the saline solution. The number of drops is soon diminished owing to the constriction of the blood-vessels.

Experiment LXXXVI. — *The Effect upon the Nervous System.*—The first experiment showed that the extract of suprarenal gland had a depressing and paralysing action upon the central nervous system.

Experiment LXXXVII. — *The Effect upon Muscle and Nerve.*—Two muscle and nerve preparations are made, and their excitability is determined in the usual manner. The nerve of the one preparation is placed in a watch-glass full of the extract of suprarenal gland and its muscle is left outside. The muscle alone of the other preparation is placed in the watch-glass. The excitability is tested from time to time, but no marked change will be observed.

Schäfer and Oliver showed that the period of relaxation of a muscle is much prolonged by the action of suprarenal extract.

The Action of Drugs upon the Contraction of the Frog's Heart

Before the classical work of Gaskell upon the contraction of the heart in the frog and the tortoise, the effects of various drugs were attributed chiefly to a stimulating or paralysing action, as the case might be, upon the ganglia and nerves of the heart. It will be of value, therefore, to consider the action of drugs upon the heart in the light of Gaskell's discoveries.

The old view of the contraction of the heart was this: Remak's ganglia in the sinus venosus were supposed to be a motor centre, which sent out impulses to the muscle of the auricles and ventricle; Bidder's ganglia at the junction of the auricles and ventricle were supposed to act as a co-ordinating centre, whereby the sequence of the contraction of the auricles and ventricle after the beat of the sinus was maintained.

This latter centre was also believed to act as a less excitable motor centre.

The first Stannius'[1] ligature, between the sinus and the auricles, was said to produce standstill of the heart by removing the action of the motor centre, or Remak's ganglia; the second Stannius' ligature, between the auricles and ventricle, caused the ventricle to beat again, because it stimulated the subordinate motor centre in Bidder's ganglia.

Gaskell has shown that the beat of the heart depends upon the greater rhythmic power of the sinus as compared with the other portions of the heart. The sequence of contraction in the sinus, auricles and ventricle is due to the passage of the contraction, which begins in the sinus, over tissue of less conductivity; there is, therefore, a pause in the passage of the wave from sinus to auricles, and from auricles to ventricle, owing to the blocks at the junction of the various chambers. In the dying heart, or by changes artificially produced, the block between the auricles and ventricle is increased, so that every auricular contraction does not pass (see Fig. 67). The sinus and auricles often continue to contract for a long time after the ventricle has ceased to beat (see Fig. 46), and the sinus beats after the auricles have come to a standstill.

The first Stannius' ligature produces standstill of the auricles and ventricle, because it cuts off the contraction of the more excitable sinus from the less excitable tissue of the auricles and ventricle. In time the auricles and ventricle beat with their own rhythm, and these contractions can be initiated by the second Stannius' ligature, which, tied round the auriculo-ventricular groove, will damage some of the fibres, and cause in the adjoining parts sub-excitation sufficient to facilitate the independent contraction of the auricles and ventricle.

The vagus nerve is to be considered as a nerve produc-

[1] P. 10.

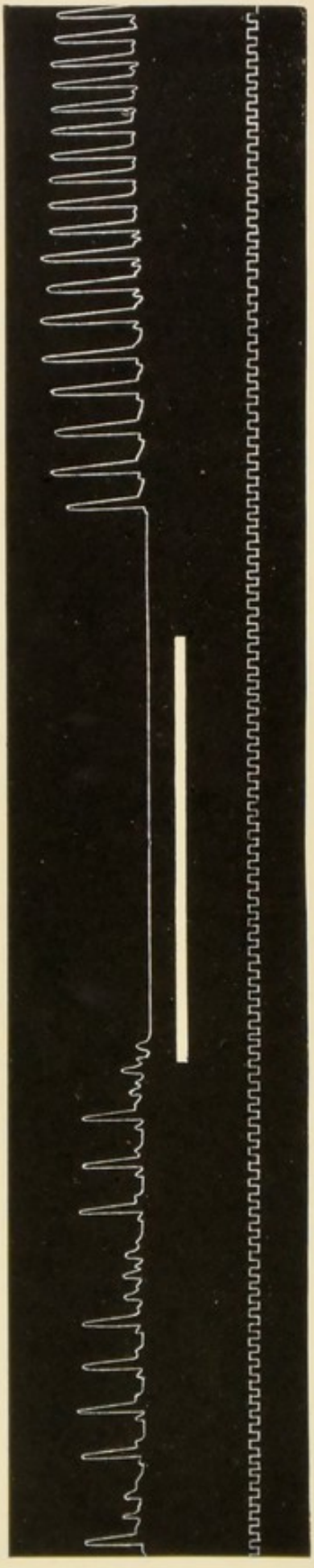


FIG. 67.—Contraction of a frog's heart. The heart was beating irregularly from the commencement of the experiment; no drug was used. The beat was improved for a few seconds by the application of normal tap-water saline solution. During the time marked by the horizontal line, the vago-sympathetic nerve was stimulated by a strong faradising current; standstill was produced and was followed by a marked improvement in the beat of the heart. Temperature of air = 21°. The time is marked in seconds.

ing, not only a standstill of the heart in diastole, but also a change in its nutrition, a storing up of combustible material or *anabolism*. The after-effect of the stimulation of this nerve is a more powerful contraction, and the restoration of a normal sequence in the contraction of the various chambers of the heart, if the beat had been previously so irregular that a ventricular contraction did not follow that of the auricles; the improvement in nutrition removes a block (Fig. 67). The sympathetic nerve, on the other hand, causes acceleration of the beat of the heart (Fig. 7), and increased destruction of combustible material or *katabolism*.

Further, Gaskell has shown that the ganglion-cells of the heart are to be looked upon simply as peripheral efferent nerve-cells connected with the inhibitory fibres of the vagus nerve; the fibres of that nerve are medullated when they enter the heart, but non-medullated fibres are found in the auricles and ventricle. The accelerator fibres in the white rami communicantes

from the second, third and fourth thoracic nerves are medullated, and are related to the ganglion stellatum, from which issue the non-medullated accelerator fibres, which form the sympathetic nerve passing to the heart.

The action of drugs applied to the heart of a pithed frog may be due to the influence of the drug upon (1) the nervous elements in the heart, or (2) the muscle-substance of the heart, or (3) both of these tissues.

The Influence of Drugs upon the Nervous Elements of the Heart.—The drug may act upon the pre-ganglionic fibres, upon the post-ganglionic fibres, or upon all the nervous tissue found in the heart (Fig. 70). Different drugs select different parts, and the same drug may, according to the strength of the dose, act upon one or all of the nervous elements. Thus it has been shown (Expt.

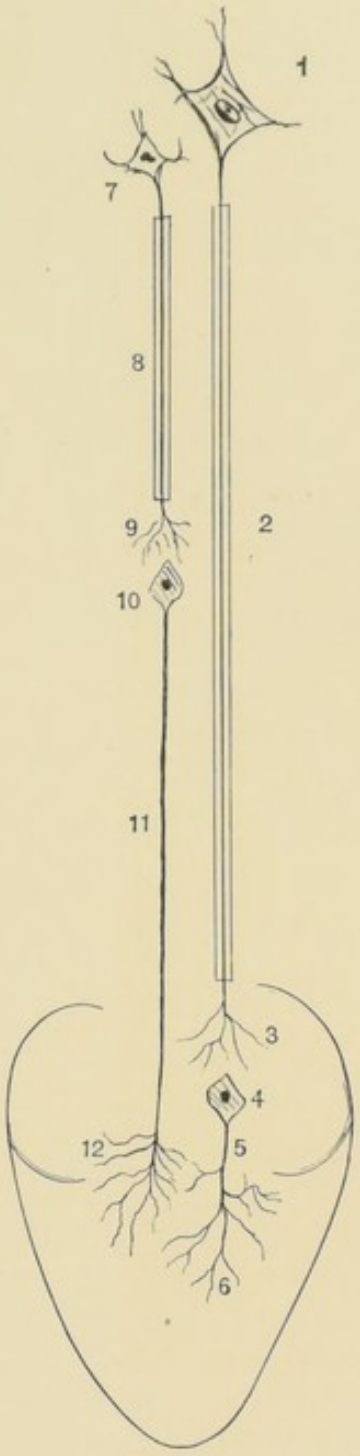


FIG. 68.—Diagram of the nerves of the heart. 1, Nerve-cell of the vagus centre in the medulla oblongata. 2, Medullated inhibitory fibre of the vagus. 3, Its termination around a ganglion-cell. 4, In the heart. 5, Post-ganglionic non-medullated fibre and its termination. 6, In the muscular tissue of the heart. 7, Ganglion-cell giving rise to the medullated accelerator fibre. 8, In the white ramus communicans. 9, The termination around the nerve-cell. 10, Of the ganglion stellatum. 11, The post-ganglionic non-medullated nerve fibre and its terminations. 12, In the muscular tissue of the heart. The heart is roughly indicated in outline.

LII.) that nicotine at first paralyses the pre-ganglionic fibres of the vagus, so that stimulation of the vago-sympathetic nerve with a strong faradising current produces no standstill, but acceleration; at this stage, however, the application of the electrodes to the sinus will cause standstill owing to the excitation of the post-ganglionic fibres of the vagus (Fig. 41). The further action of a strong dose of the drug is to paralyse all the nervous elements of the heart, and the contractions are extremely slow and may cease altogether, owing to the direct action of the drug upon the muscle-fibres; stimulation of the sinus now causes a series of beats (Fig. 42), for the muscle still responds to stimulation.

In a similar manner curare (Expt. L.) acts on the pre-ganglionic fibres around the nerve-cells before it acts upon the junction of the post-ganglionic fibres with the cardiac muscle.

It has been shown (Expt. LVI.) that after very small doses of atropine stimulation of the vagus nerve and of the sinus will not produce inhibition; the drug paralyses the terminations of the post-ganglionic fibres of the vagus.

The Influence of Drugs upon the Muscle-Substance of the Heart.—The action of drugs upon the muscular fibres of the heart may be either to increase or diminish the contraction of the heart; the drug may act tonically or atonically. A good example of the former class is digitaline (Expt. LXXVI.); of the latter, muscarine (Expt. LXVIII.). A strong dose of digitaline causes the heart to pass into a firmly contracted condition and kills it in the systolic phase; on the other hand, muscarine causes the heart to cease beating in a relaxed condition, in the phase of diastole.

Veratrine and caffeine also act tonically upon the muscle of the heart (Expts. LXXIII. and XLIV.).

The Influence of Drugs upon both the Nervous and Muscular Tissues of the Heart.—Many of the drugs which act most readily upon the nervous elements of the heart attack the muscular tissue if their action be prolonged or the dose be increased. This can be observed in the case of atropine:

weak doses produce little alteration in the beat of the heart, but rapidly paralyse the post-ganglionic fibres of the vagus (Expt. LVI.); further doses act on the muscle and lengthen the duration of the contraction (Fig. 44).

Nicotine and curare also show an action first upon the nerves and then upon the muscle.

Antagonism.—In the experiments upon muscarine and pilocarpine, it has been shown that the effects of the drug upon the heart can be removed by the action of atropine, and that further doses of muscarine, or pilocarpine, as the case may be, will again produce a slower and more feeble beat. Such an action is known as *antagonism*, and the drugs are said to be *antagonistic*. In true cases of antagonism, the opposed action is mutual; the action of the one drug can be reversed by the other, and that of the other by the one. An *antidote* is a remedy which counteracts the effect of a poisonous substance, but it is not necessarily a true antagonist; thus chalk is an antidote to oxalic acid, because it forms an insoluble chemical compound. In the case of most antagonists, there is no evidence of direct chemical interaction; the two poisons mixed in a glass vessel do not form an inert chemical compound, but remain a mixture of the two poisons. The explanation of antagonism may possibly be found in different chemical changes set up in the tissues by the drugs. Strychnine affects the nerve-cells, and causes increased excitability and convulsive discharges of nervous impulses; chloral hydrate diminishes the excitability and paralyses the nerve-cells; the one drug is the antagonist of the other, and in appropriate doses will counteract its effects. This antagonism, however, is by no means so complete as that of atropine and pilocarpine, or that of atropine and physostigmine.[1]

[1] See p. 91.

Comparison of Ordinary Doses and Lethal Doses in the Frog and in Man.

Drug.	Frog.		Man.	
	Ordinary Dose.	Lethal Dose.	Ordinary Dose.	Lethal Dose.
Alcohol	5♏ (0·296 c.c.)	10♏ (0·592 c.c.)	Varies with different individuals	5ʒ (142·1 c.c.)
Ether	5♏ (0·296 c.c.)	10♏ (0·592 c.c.)	10 to 60♏ (0·592 c.c. to 3·55 c.c.)	...
Chloroform	5♏ (0·296 c.c.)	8♏ (0·474 c.c.)	1 to 5♏ (0·059 to 0·296 c.c.)	1 to 2ʒ (28·42 to 56·84 c.c.)
Chloral hydrate	$\frac{1}{6}$ grain (0·013 grm.)	$\frac{2}{3}$ grain (0·026 grm.)	5 to 20 grains (0·324 to 1·296 grm.)	180 to 460 grains (11·660 to 29·9 grm.)
Strychnine	$\frac{1}{7000}$ grain (0·00009 grm.)	$\frac{1}{3000}$ grain (0·00022 grm.)	$\frac{1}{600}$ to $\frac{1}{15}$ grain (0·00108 to 0·0043 grm.)	$\frac{1}{2}$ to 2 grains (0·032 to (0·130 grm.)
Hydrastine hydrochlorate	$\frac{1}{10}$ grain (0·0065 grm.)	$\frac{1}{8}$ grain (0·008 grm.)	$\frac{1}{4}$ to 1 grain (0·016 to 0·065 grm.)	...
Morphine acetate	$\frac{1}{2}$ grain (0·032 grm.)	$1\frac{1}{3}$ grain (0·087 grm.)	$\frac{1}{8}$ to $\frac{1}{2}$ grain (0·008 to 0·032 grm.)	$\frac{1}{2}$ grain to 1 grain (0·032 to 0·065 grm.)
Caffeine	$\frac{1}{10}$ grain (0·0065 grm.)	$\frac{1}{5}$ grain (0·013 grm.)	1 to 5 grains (0·065 to 0·324 grm.)	200 grains (12·96 grm.)
Curare	$\frac{1}{1000}$ grain (0·00065 grm.)	$\frac{1}{300}$ grain (0·0013 grm.)	$\frac{1}{200}$ to $\frac{1}{2}$ grain (0·0032 to 0·032 grm.)	...
Nicotine	$\frac{1}{200}$ grain (0·0032 grm.)	$\frac{1}{2}$ grain (0·032 grm.)	$\frac{1}{6}$ to 1 grain (0·011 to 0·065 grm.)	...
Atropine sulphate	$\frac{3}{4}$ grain (0·049 grm.)	$1\frac{1}{2}$ grain (0·097 grm.)	$\frac{1}{2000}$ to $\frac{1}{1000}$ grain (0·00032 to 0·00065 grm.)	2 grains (0·13 grm.)
Cocaine hydrochlorate	$\frac{1}{500}$ grain (0·0013 grm.)	$\frac{1}{200}$ grain (0·0032 grm.)	$\frac{1}{5}$ to $\frac{1}{2}$ grain (0·013 to 0·032 grm.)	22 to 32 grains (1·426 to 2·074 grm.)
Pilocarpine nitrate	1 grain (0·065 grm.)	$1\frac{1}{2}$ grain (0·097 grm.)	$\frac{1}{200}$ to $\frac{1}{2}$ grain (0·0032 to 0·032 grm.)	...
Muscarine	...	$\frac{1}{10}$ grain (0·0065 grm.)	Not used in medicine	...
Veratrine	$\frac{1}{2000}$ grain (0·00032 grm.)	$\frac{1}{64}$ grain (0·001 grm.)	$\frac{1}{64}$ to $\frac{1}{16}$ grain (0·001 to 0·004 grm.)	...
Digitaline	...	$\frac{1}{200}$ grain (0·0032 grm.)	$\frac{1}{1000}$ to $\frac{1}{300}$ grain (0·00065 to 0·0022 grm.)	...
Physostigmine sulphate	$\frac{1}{10}$ grain (0·0065 grm.)	$\frac{1}{5}$ grain (0·013 grm.)	$\frac{1}{600}$ to $\frac{1}{200}$ grain (0·00108 to 0·0032 grm.)	...
Suprarenal gland	5 grains (0·324 grm.)	...	5 to 15 grains (0·324 to 0·972 grm.)	...

The weight of a frog is 20 to 30 grm.; that of an adult man, 70,000 grm.

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