with those here reported indicate that the stimulating activity of penicillin and streptomycin evident *in vitro* is probably operative *in vivo*.

Discussion. By evincing, in suitable concentrations, bacteriostatic or bactericidal activity and at certain much lower concentration levels a stimulatory effect, penicillin and streptomycin conform to a familiar behavior pattern of drugs and chemical reagents. The biphasic action of sulphonamides has been reported.[1] Recognition of the potential stimulatory activity of these drugs further increases the problems of initial dosage and maintenance in the body fluids of proper drug levels. The importance of achieving complete destruction of the infective agent by the initial dosages receives added emphasis. It is apparent also that concentrations of these drugs efficacious as bactericidal or bacteriostatic agents for one species of microorganism, for another, perhaps coexistent infective agent, may be stimulatory. Thus, Eagle *et al.*[3] found that 0.01-0.02 u/ml of penicillin was actively spirochaeticidal, a zone not infrequently stimulating to the spore-forming species employed in our study. Rammelkamp and Keefer[4] reported maximum antibacterial action for *Streptococcus haemolyticus* when the concentration of penicillin in blood and serum was 0.019 u/ml. Evidence[5,6] seems to indicate that part of the therapeutic activity of penicillin is associated with accompanying impurities, a fact which has necessitated in recent years the administration of larger doses to offset the greater refinement of the product; conversely it is not unlikely that the stimulatory concentration level of penicillin and streptomycin would be lowered by increased purification.

Summary. Suitable, low concentrations of penicillin or streptomycin in sterile milk (autoclaved) stimulated the growth of many spore-formers and *Staphylococcus aureus* and *Streptococcus agalactiae*. The degree of stimulation differed with the organism and with some cultures was not apparent in the range of concentrations used; some of the practical implications of growth stimulation by penicillin and streptomycin are briefly discussed.

[3] Eagle, H., Magnuson, H. J., and Fleischman, R., *Johns Hop. Hosp. Bull.*, 1946, **79**, 168.

[4] Rammelkamp, C. H., and Keefer, C. S., *J. Clin. Invest.*, 1943, **22**, 649.

[5] Smith, W. J., *Science*, 1946, **104**, 411.

[6] Comm. Med. Res., U. S. P. H. and F. D. A., *J. Med. Assn.*, 1946, **131**, 271.

15754

Studies on Auricular Tachycardia Caused by Aconitine Administration.

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Aconitine in minute amounts provokes abnormal stimulus formation in the heart. It has been demonstrated that with particular precautions a long-lasting, regular, bigeminal rhythm can be obtained after the intravenous administration of aconitine in the experimental animal.[1] Studies on the effect of topical application of aconitine on the dog's heart are reported in this paper.

Method. The experiments were performed on 23 dogs. Morphine-nembutal anesthesia was used. The heart was exposed in the usual way. The vagi were severed in the neck. If necessary, the peripheral end was stimulated with the aid of a Cambridge inductorium.

The electrocardiograms were registered in lead II.

* Aided by a grant from the United Hospitals Fund.

[1] Scherf, D., *Z. f. d. ges exp. Med.*, 1929, **65**, 198, 222.

Solutions of 0.05% of "potent" aconitine crystals "Merck" were used. The injections were performed with greatest care with the aid of a tuberculin syringe. Even the small amounts of aconitine, which were used in these experiments, if introduced into the auricular cavity, caused a ventricular tachycardia and ventricular fibrillation. One must be careful not to leave any aconitine solution on that part of the auricular surface which is in contact with the ventricular wall because this also leads to a ventricular tachycardia and eventually to ventricular fibrillation. The potency of the solution quickly deteriorates, even when kept in the refrigerator.

Most of the injections were performed on the appendix of the left auricle, a few millimeters below its tip. Injections into the wall of the appendix of the right auricle had the same result.

Experimental results. Injection of 0.05 cc of a solution of 0.05% of aconitine into the wall of the auricles of the dog's heart leads to a prolonged regular auricular tachycardia. The tachycardia begun within 90 seconds after the injection. The rate varied between 196 and 310 per minute. The tachycardia lasted between 40 and 60 minutes, and was therefore sufficiently long to permit certain studies to be made.

In these experiments the following facts could be demonstrated:

1. Faradic stimulation of the right or left vagus nerve during the auricular tachycardia led to a remarkable acceleration of the rate of the auricle in all experiments. This acceleration often amounted to an increase of more than 100%. The acceleration was immediate, and after the end of stimulation, the former rate returned within a few seconds in the form of a rapid but not abrupt decline. The auricular waves remained unchanged in the electrocardiogram, or showed only the slight alterations which would be expected with an increase in rate. No difference could be detected in the results when right and left vagus were stimulated respectively. Observation of the right auricle during the vagus stimulation revealed an immediate disappearance of the strong fluttering movements, and on close observation, weaker, but rapid and regular undulatory movements could be detected. A varying degree of auriculo-ventricular block appeared. Auricular fibrillation, or rapid reexcitation of the auricles with rates up to 3500 per minute was never observed. In only one experiment did auricular fibrillation appear following the injection of aconitine and before stimulation of the vagi.

2. Clamping off the appendix of the auricle into which the injection was made, invariably led to an immediate disappearance of the tachycardia and the reappearance of sinus rhythm. In some instances coronary sinus rhythm with deep inverted P waves was noted; this was soon followed by regular sinus rhythm. Removal of the clamp permitted the tachycardia to reappear within a few seconds.

3. Stimulation of the vagus while the clamp was in position led to a complete cardiac standstill. Only in the clamped-off appendix of the left auricle were fine undulatory movements visible.

4. Cooling the focus of origin of the tachycardia, that is the area where the injection had been made, with a thermode also caused the tachycardia to vanish for the duration of the cooling. The tachycardia recurred immediately and invariably with the removal of the thermode.

Fig. 1a shows at the beginning a regular tachycardia caused by the injection of aconitine in the manner described in the appendix of the left auricle. A rate of 230 auricular and ventricular beats per minute is present. The R waves are so thin that they are scarcely visible. The P waves are tall. After the 10th beat the left vagus was stimulated in the neck with a strong faradic current. The auricular rate immediately increased to 428 beats per minute without any change in the form of the auricular waves. An auriculo-ventricular block appeared and made it easier to observe the auricular electrocardiogram. The vagal stimulation was stopped a few seconds later (first third of the tracing in Fig. 1b, which is a direct con-

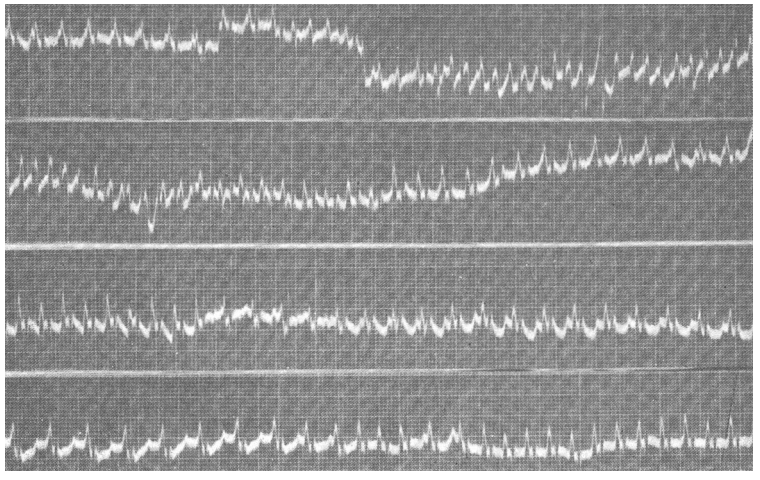
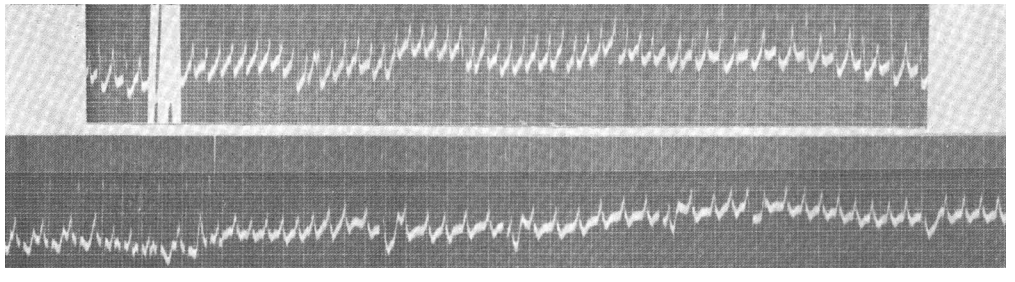


FIG. 1, a-d.
The top tracing (Fig. 1a) shows at the beginning an auricular tachycardia and the effect of vagus stimulation which begins in the middle of the tracing. Fig. 1b shows the end of the vagus stimulation (middle of tracing). In the beginning of tracing 1c the site of stimulus formation was clamped off; in the middle of Fig. 1d the clamp was removed (Lead II).

a



b

FIG. 2a and 2b.
The signal indicates the beginning of vagus stimulation. Fig. 2b shows a slight irregularity of the auricle during vagus stimulation (Lead II).

tinuation of Fig. 1a). Without delay the same tachycardia with a rate of 230 was again registered as in the beginning of Fig. 1a. In the first third of Fig. 1c, the appendix of the left auricle was clamped, so that the site of injection was isolated from the rest of the heart. A sinus rhythm appeared immediately with a rate of 187 beats per minute and soon the rate fell to 156. The clamp was removed a few seconds later (middle of Fig. 1d, which is a direct continuation of Fig. 1c), and an auricular tachycardia reappeared with a rate of 250 beats per minute.

Fig. 2a shows at the beginning a few complexes of a tachycardia with a rate of 200 which appeared following an injection of the same quantity of aconitine into the medial wall of the left auricular appendix. The broad, wide, irregular line represents a signal indicating the beginning of stimulation of the left vagus nerve. During the stimulation of the vagus the auricular rate rose immediately to 461 and there was almost complete inhibition of the auriculo-ventricular conduction. The cessation of vagus stimulation was followed by an immediate recurrence of the

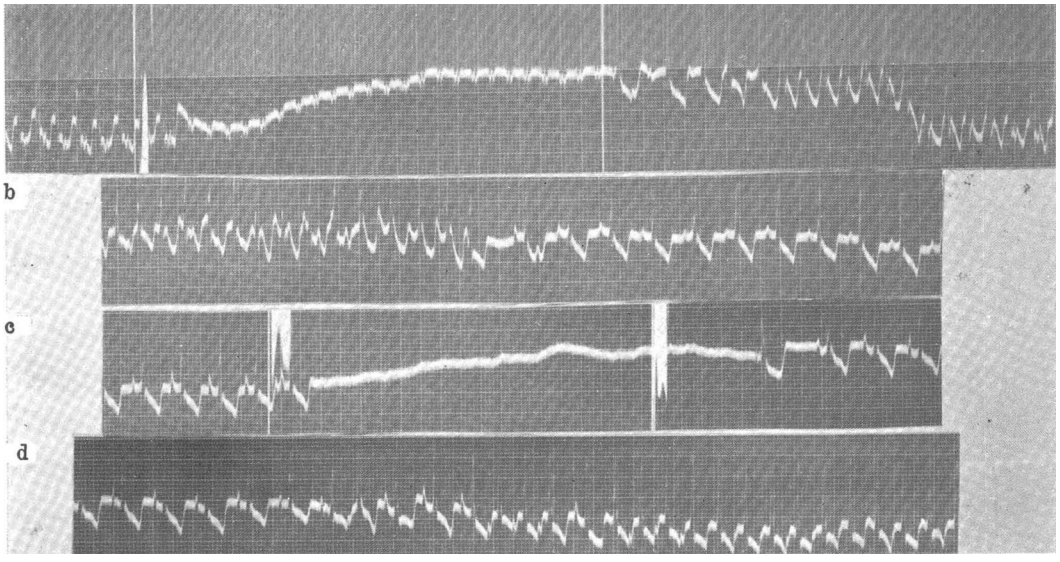


FIG. 3, a-d.
Vagus stimulation during auricular tachycardia (Fig. 3a), clamping off the focus in the right auricle (Fig. 3b), vagus stimulation during presence of clamp (Fig. 3c), and removal of clamp (Fig. 3d) (Lead II).

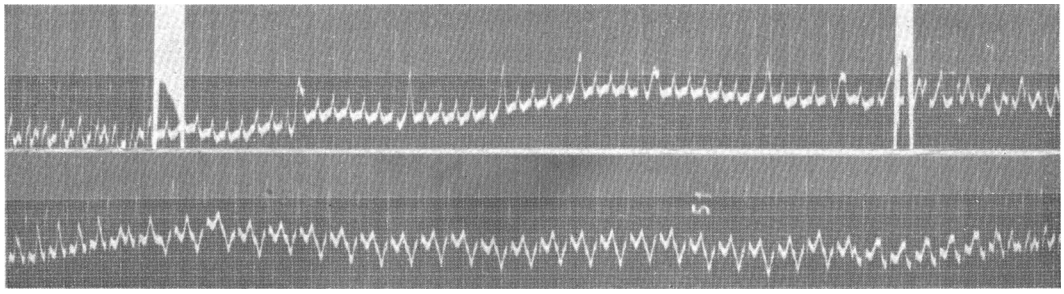
former tachycardia with a rate of 200 beats per minute.

Only rarely was the auricular tachycardia during vagus stimulation irregular. In Fig. 2b, which was secured in another experiment than Fig. 2a, at the beginning of the tracing the auricular rate after administration of aconitine was again 200. During stimulation of the right vagus nerve the rate increased to an average of 428 beats per minute and slight arrhythmias were visible. Temporary interruption of the contact of the stimulating electrode with the vagus nerve could not be excluded.

Fig. 3 is from an experiment in which the aconitine was injected on the tip of the right auricular appendix. A tachycardia with a rate of 272 appeared within a few seconds (Fig. 3a). Faradic stimulation of the right vagus led to an increase of rate to 375 beats per minute (Fig. 3a), and to a complete inhibition of the auriculo-ventricular conduction. The 2 perpendicular white lines represent signals showing the beginning and the end of the vagal stimulation. After stimulation was stopped a short period of 2:1 block is noted (Fig. 3a), and the regular tachycardia with a rate of 280 recurred. Clamping off the right auricular appendix caused a sinus rhythm to appear immediately (Fig. 3b) with a rate of 150. In Fig. 3c, the effect of the vagus stimulation during the clamping, and the existence of a sinus rhythm is demonstrated; a complete standstill of the heart resulted, without any sign of activity in the electrocardiogram. Removal of the clamp permitted the tachycardia to recur immediately in the same form as before with a rate of 214 (Fig. 3d).

Fig. 4 was obtained in an experiment in which the injection was made on the appendix of the left auricle. A tachycardia with a rate of 310 appeared, and the rate increased during the vagus stimulation (see signals) only to 375 (Fig. 4a). Cooling of the site of origin of the tachycardia (the area of injection) led to the immediate disappearance of the tachycardia (Fig. 4b). A regular coronary sinus rhythm with a rate of 187 was present. Interruption of cooling was immediately followed by reappearance of the tachycardia, at the end of Fig. 4b. Usually

a



b

FIG. 4a and 4b.
Vagus stimulation during auricular tachycardia (Fig. 4a) and cooling of area of injection (Fig. 4b) (Lead II).

cooling led to the appearance of sinus rhythm. The response to cooling was, in general, the same as to clamping off of the area of injection.

In most experiments all these measures, such as vagus stimulation, clamping, and cooling, were performed 3 or 4 times in succession, and always with the same results.

Discussion. Of paramount importance in the evaluation of these experiments is the question as to whether the tachycardias caused by the injection of aconitine represent an auricular tachycardia of the "essential paroxysmal tachycardia" type, or whether we are dealing with auricular flutter. This differentiation is often impossible and in recent years many arguments have been presented in favor of the identity of these conditions. It is the opinion of the author that for the time being a separation is necessary, and that the facts in favor of their identity are too few and not really crucial.

The tracings appear similar to those published by many authors as examples of experimental auricular flutter.[2-5] The isoelectric line between the single auricular waves is short or absent. Flutter rates in the dog's auricles however, were found to vary between 345 and 580[6] while the rate in the experiments reported in this paper was definitely below this range before vagus stimulation and within it during stimulation. Against the diagnosis of a simple tachycardia like the essential paroxysmal tachycardia in man there is the observation that stimulation of either vagus nerve with even the strongest faradic current never caused sudden ending of the tachycardia. This sudden abolition of an auricular tachycardia is seen however in only a certain percentage of essential paroxysmal tachycardia, and absence of this effect does not invalidate the diagnosis. It is entirely possible that the inability to end the tachycardia by vagal stimulation is due to the special conditions which led to the tachycardia in this experiment. Against the existence of auricular flutter in these tracings, the argument may be used that it was never possible, even with the strongest current, to change the auricular tachycardia into auricular fibrillation by vagus stimulation. One easily succeeds in doing this in auricular flutter caused by other means.[4,7] The phenomenon of rapid reexcitation with auricular rates between 1500 and 3500 per minute rarely occurs during vagus stimulation

2 Lewis, T., Drury, A. N., and Bulger, H. A., *Heart*, 1921, **8**, 83.

3 Lewis, T., Drury, A. N., and Bulger, H. A., *Heart*, 1921, **8**, 141.

4 Rothberger, C. J., and Winterberg, H., *Arch. f. d. ges. Physiol.*, 1914, **160**, 42.

5 Scherf, D., *Z. f. d. ges. exp. Med.*, 1928, **61**, 30.

6 Lewis, T., Feil, H. S., and Stroud, W. J., *Heart*, 1918/20, **7**, 191.

7 Lewis, T., Drury, A. N., and Iliescu, C. C., *Heart*, 1921, **8**, 311.

unless the flutter rate before the stimulation is over 400 per minute.[7] The gradual but rapid increase and decline of the auricular rate which has been observed in instances of auricular flutter during and after vagus stimulation[4] is very similar to the phenomenon reported here.

In view of all these facts, it seems that a definite decision is impossible and the presence of either type of auricular tachycardia cannot be definitely ruled out.

A paradoxical increase in the formation of auricular and ventricular extrasystoles after vagus stimulation in the dog following intravenous injection of aconitine has been described as a regular phenomenon. Intravenous injection of choline preparations had the same effect.[1] The increase in the number of auricular extrasystoles in these experiments occurred however only *after* the stimulation of the vagus; during the stimulation only the usual inhibition of the auricles with standstill was seen.

The phenomenon of reexcitation and the marked increase of rate of the auricles, during vagus stimulation was used by Lewis and his associates in brilliant studies[3,6,7] as one of the more important facts supporting the theory of circus movement. The shortening of the refractory phase during the stimulation of the vagus, which may amount to more than 1/5 of the normal, abolishes barriers in the form of islands of refractory muscle in the way of the circulation "Mother" wave and causes this wave to use a less sinuous path and therefore to circulate faster. Another possibility considered by Lewis would be the utilization of another path which is shorter than the original one around the orifices of the great veins.

One must concede that the circus movement theory explains both phenomena, the moderate increase of rate during vagus stimulation, as in the experiments reported here, and the appearance of the rates of over 3000 per minute, better than any other theory.[8] A simple increase of the rate of stimulus formation is difficult to accept in view of the high rates which occur in rapid reexcitation and in view of the known inhibitory action of the vagus on the heart. Rothberger and Winterberg, who explained flutter by a rapid stimulus formation in a single center, also tried to correlate the phenomenon of rapid reexcitation during vagus stimulation with a shortening of the refractory period; the finer mechanisms however are still unexplained. There is no information about the influence of vagus stimulation on the formation of stimuli in the centers, and it is possible that an increase of the rate of stimulus formation during vagus stimulation is a typical consequence of the shortening of the refractory period.

The observation that clamping off the site of origin of the tachycardia or cooling the point of injection of the aconitine abolished the tachycardia and immediately reintroduced sinus rhythm is of interest in connection with the 2 viewpoints regarding the mechanism of origin of auricular flutter. Still more important is the fact that interruption of the cooling causes the tachycardia immediately to reappear. These observations are not easily explained by a circus mechanism. It has been maintained that localized circus movements occur and cause localized auricular fibrillation which can be interrupted by clamping off or cooling a small area.[9] The path of such a small circulating wave was estimated to use a circuit with a diameter of only 2.5 to 3.8 mm.[7] If such a localized circus movement exists in these experiments however, it is hard to understand how interruption of the cooling is immediately followed by the reappearance of the same tachycardia as before. Without the assumption of a heterotopic focus of stimulus formation, this observation is difficult to explain.

Thus, in conclusion, one may state that if we are dealing with auricular flutter in these experiments, the effect of the cooling of the area into which the solution of aconitine was injected argues against the assumption of a circus movement. If we are dealing with a heterotopic tachycardia, the appearance of an acceleration of rate during

[8] Garrey, W. E., *Physiol. Rev.*, 1924, **4**, 215.

[9] McWilliam, J. A., *Proc. Roy. Soc., London, Ser. B*, 1918, **90**, 302.

vagus stimulation not based on a circus movement mechanism is of interest.

Summary. Focal application of aconitine to the dog's auricle in the form of a subepicardial injection is followed by the appearance of a prolonged regular tachycardia with a rate of approximately 200 to 300 beats per minute. Faradic stimulation of the vagus nerves in the neck always leads to a remarkable increase of rate of the auricles. Auricular fibrillation or the phenomenon of rapid reexcitation were never observed during the vagus stimulation.

Separation of the site of injection from the rest of the heart by clamping abolishes the tachycardia; it regularly reappears on removal of the clamp. Cooling of the site of injection by a thermode also stops the tachycardia, and it reappears immediately when cooling is discontinued.

The tachycardia shows characteristics of auricular flutter, but auricular tachycardia of the type "essential paroxysmal tachycardia" cannot be ruled out.

The results of the experiments cannot be explained under the assumption that the tachycardia is caused by a circus movement. Therefore the increase of rate during the vagus stimulation requires another explanation than the one given by Lewis.

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A Method for Intrathoracic Operation on the Rat.*

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Positive control of intrapulmonary tension and oxygenation is highly desirable for intrathoracic operations on any animal. The technic for larger animals, such as dogs, is well standardized, but because of the small size of the laboratory rat, none of the methods could be satisfactorily used in intrathoracic operations on that animal.

In connection with problems involving pneumonotomy and pneumonectomy in the rat, a simple and satisfactory method of positive pressure administration of oxygen has been evolved utilizing tracheal intubation. The rat is anesthetized with pentobarbital sodium intraperitoneally at a dosage of 30 mg per kg of body weight. In combination with this is given scopolamine hydrobromide, in a dosage of 0.6 mg for a 300 to 400 g rat.[1] The latter drug was found to increase rapidity and depth of anesthesia, reduce tracheal secretions and counteract the respiratory depression that pentobarbital sodium tends to produce. The pharynx is cleared by suction and the trachea is intubated with a special tube to be described later. The end of the tube is then connected to the oxygen line and valve apparatus. Respiration is not artificial but is performed in the natural manner with the rat working against a variable pressure water valve.

The intratracheal tube is constructed of plastic tubing† having an outside diameter of 0.08 inch (0.20 cm) and an inside diameter of 0.045 inch (0.11 cm) (Fig. 1). One end is sealed off by rotating in a gentle flame and molding with the fingers, and a slight point is produced by grinding with an emery wheel. Just above the point 3 small holes, staggered around the circumference, are cut with fine scissors and ground smooth with

* Work done in the laboratory of, and under the direction of, Dr. George M. Higgins, Division of Experimental Medicine, Mayo Foundation, Rochester, Minn.

1 Holck, H. G. O., Dosage of Drugs for Rats, in Griffith, J. Q., Jr., and Farris, E. J., *The Rat in Laboratory Investigation*, Philadelphia, J. B. Lippincott Company, 1942, chap. 13, pp. 297-350.

† Transflex, courtesy of the manufacturer, The Irvington Varnish and Insulator Company, Irvington, N.J.