The general experience has been that strains which become resistant to penicillin lose their invasive properties as indicated by growth in whole blood.[5,6] Strains which have developed resistance to sulfonamides, however, retain this capacity unchanged.[7] From the present observations it appears that, like the latter, organisms resistant to streptomycin may also retain their virulence. In addition, such strains may preserve the ability to maintain their invasiveness upon prolonged artificial cultivation to a greater extent than the parent, nonresistant culture. The clinical implications of these observations that invasiveness may be maintained and retained are evident. The development of streptomycin resistance should be reduced to a minimum through the use of a dosage schedule which will ensure early, adequate blood levels. In the light of these studies, an adequate level must be defined in terms of the specific susceptibility of the organism plus its potential ability to acquire resistance. The level of tolerance to streptomycin as well as the rate at which this tolerance is acquired are important factors and a large margin of safety is necessary.

Summary. 1. Resistance to streptomycin can be induced by repeated transfer of various organisms in streptomycin containing media. 2. In the early logarithmic stage of growth, highly resistant mutants can be isolated, by chance selection, in a single transfer. 3. In most instances, acquired resistance to streptomycin is maintained. 4. Organisms resistant to streptomycin may retain their original virulence as measured by the bactericidal test. 5. The acquisition of resistance to streptomycin with the maintenance of virulence may have certain therapeutic implications.

[5] Spink, W. W., Ferris, V., and Vivino, J. J., PROC. SOC. EXP. BIOL. AND MED., 1944, **55**, 210.

[6] Rake, G., McKee, C. M., Hambre, D. M., and Houck, C. L., *J. Immunol.*, 1944, **48**, 271.

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15748

Effect of Atabrine on Auricular Fibrillation in the Dog.

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At present there are no available data concerning the action of atabrine on cardiac muscle. However, the analogous physiological effects of quinine and atabrine in diminishing the contractibility and increasing the refractory period of striated and smooth musculature,[1] lead to a reasonable assumption that atabrine will produce similar actions to those of quinine on cardiac muscle.

Quinine and especially its more powerful isomer, quinidine, have been used for many years as a routine practice in the treatment of auricular fibrillation presumably because of their ability to prolong the refractory period in cardiac muscle and its nodal tissues as well as to decrease myocardial excitability.[2] Since recent evidence has been advanced[1,3] which clearly indicates that atabrine possesses more potent physiological and pharmacological properties when compared with quinine, it seemed most interesting to see whether atabrine would also control auricular fibrillation. Experiments in the dog were, therefore, devised to test the validity of this concept.

Methods. Five dogs were anesthetized

[1] Keogh, P., and Shaw, F. H., *Australian J. Exp. Biol. and Med. Sci.*, 1944, **22**, 139.

[2] Lewis, T., Drury, A. N., Iliescu, C. C., and Wedd, A. M., *Heart*, 1921-22, **9**, 207.

[3] Gertler, M. M., and Karp, D., *Revue Can. de Biol.*, in press.

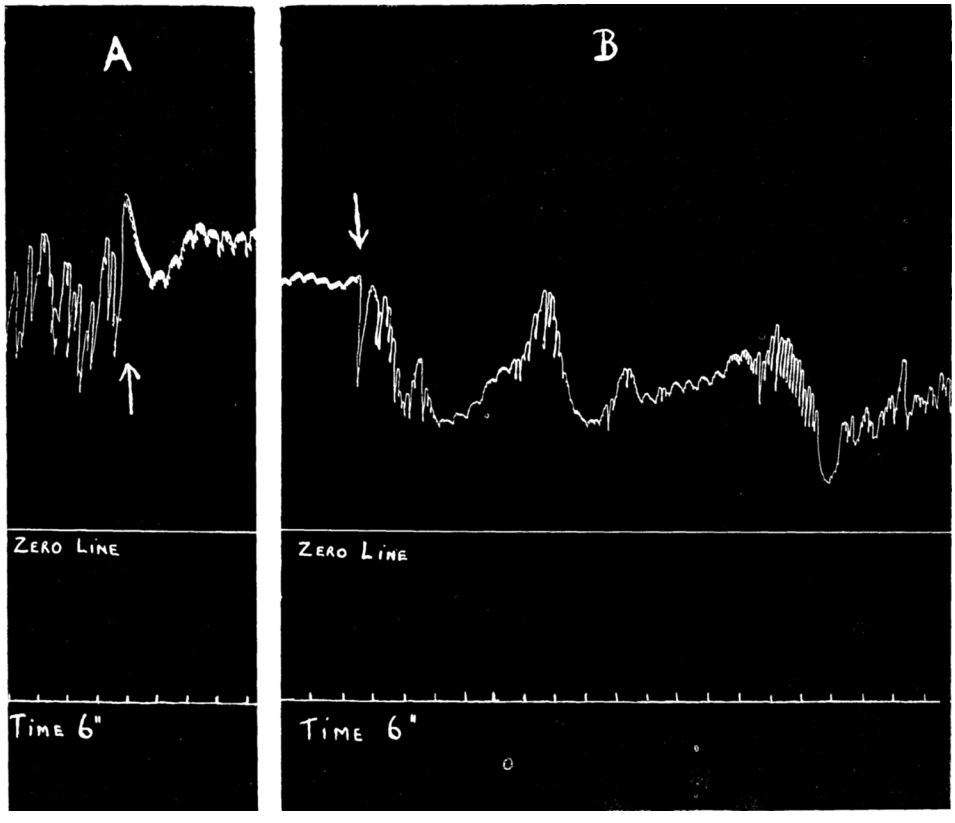

FIG. 1.
A. Restoration of normal sinus rhythm to auricular fibrillation 3 min. 24 sec. after intravenous injection of atabrine was started (Exp. 1).
B. Induction of auricular fibrillation approximately 2 hours after injection of atabrine.

with nembutal (25 mg per kg). Auricular fibrillation was produced according to the method of Hoff and Nahum.[4] Application of mecholyl (0.2% solution in normal saline) over the sino-auricular node, followed by stimulation of any region on the right auricle with a weak faradic current consistently provoked auricular fibrillation. Auricular fibrillation produced in this manner persists for at least 10 to 15 minutes and often longer. Attempts to reproduce auricular fibrillation were made immediately after its restoration to normal sinus rhythm by atabrine. One animal received 1.0 mg of eserine (physostigmine sulphate) intravenously before such an attempt was made.

A Sanborn cardiette was employed for electrocardiographic recordings. Lead II was used throughout the experiments with the animals placed in the dorsal recumbent position.

Atabrine dihydrochloride (Winthrop Chemical Co.), a 0.5% solution in normal saline, was always freshly prepared for these experiments.

Electrocardiographic and blood pressure records were taken immediately prior to and during auricular fibrillation. These records were continued during the infusion of atabrine and continued thereafter until the heart returned to its normal rhythm.

Experimental Results. The restoration of regular sinus rhythm to auricular fibrillation occurred rapidly in all the 5 animals following the intravenous infusion of atabrine (Table I). The gradual recovery to normal rhythm in Experiment 1 can be seen in the

[4] Hoff, H. E., and Nahum, L. H., *Am. J. Physiol.*, 1940, **129**, 428.

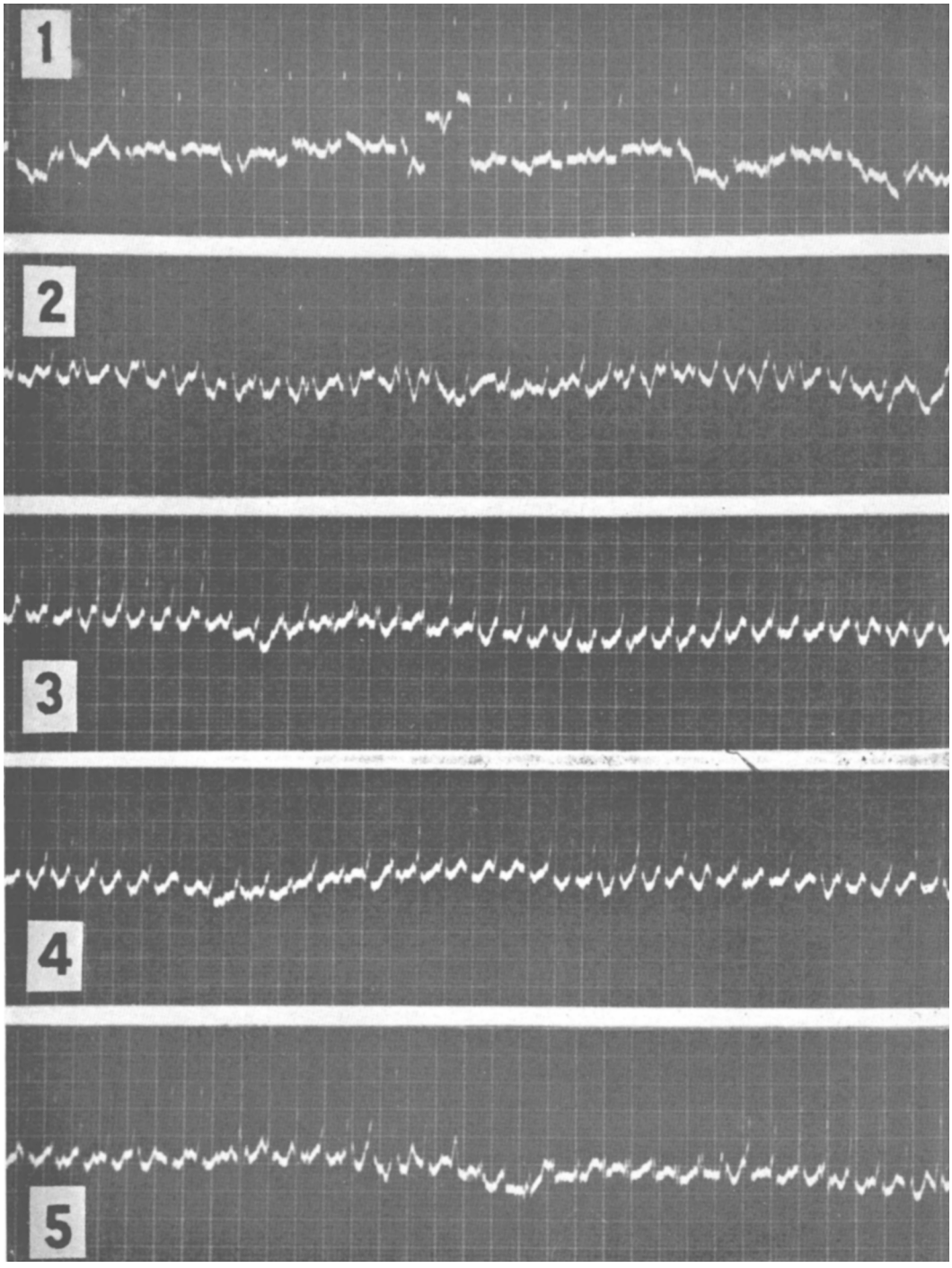

FIG. 2.

Electrocardiogram. Lead II. Same experiment as in Fig. 1. 1—Control record. Heart rate 150 at 10:30 a.m. 2—Auricular fibrillation. Heart rate 234 to 312 at 10:35 a.m. 3—Infusion of atabrine started. 4—5 mg atabrine injected. 5—5 mg atabrine injected.

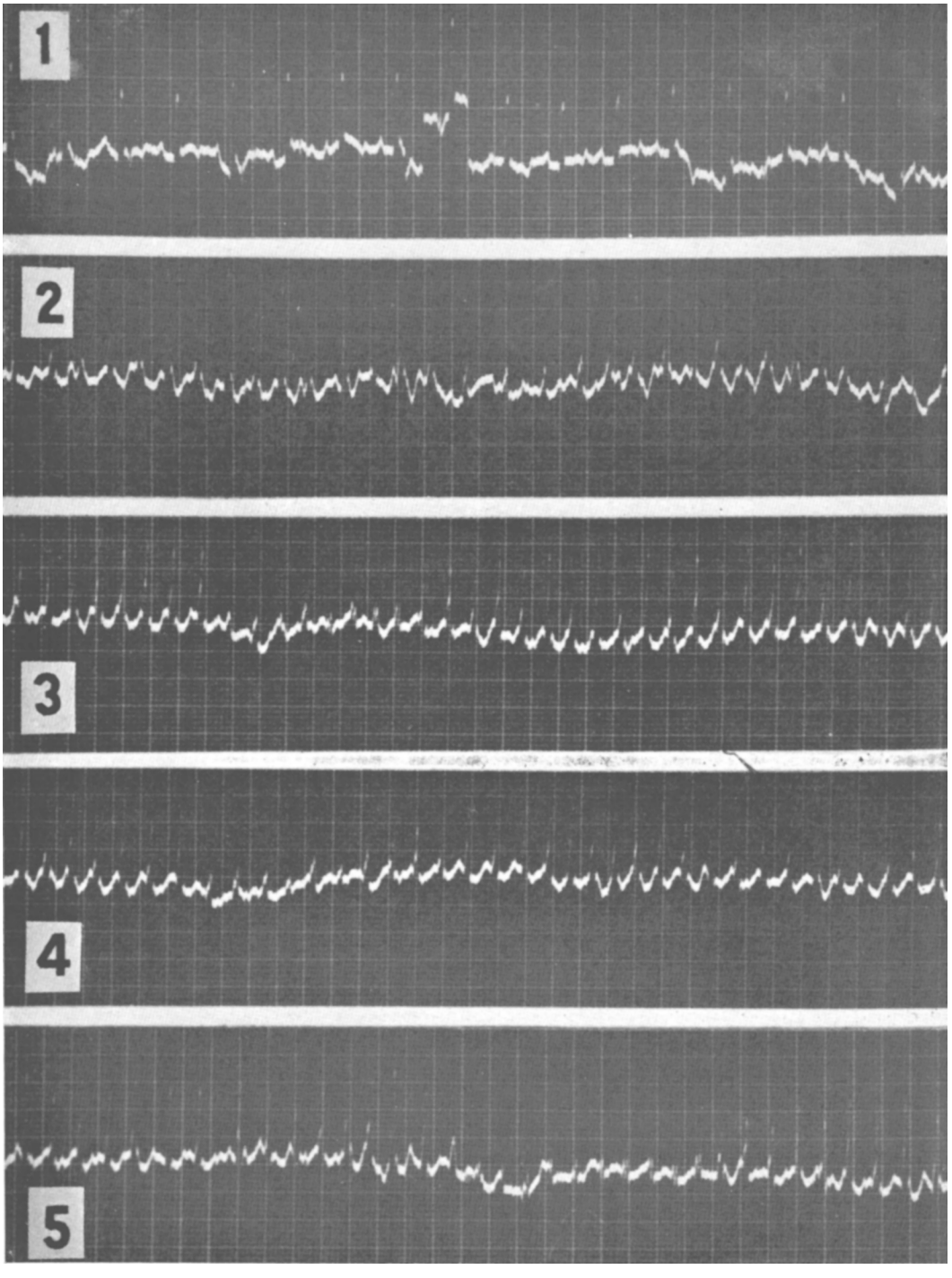

FIG. 3.

Electrocardiogram. Lead II. Continuation of Fig. 2. 6—5 mg atabrine injected. 7—5 mg atabrine injected. 8—5 mg atabrine injected. 9—7.5 mg atabrine injected. 10—Return to normal rhythm after total injection of 37.5 mg. Heart rate 167 at 10:40 a.m. See Fig. 1A.

TABLE I.

Exp. No.	Wt of dog (kg)	Total amt of atabrine (mg)	Mg/kg
1	15	30.0	2.0
2	26	37.5	1.44
3	13.6	40.0	2.94
4	12.5	33.5	2.65
5	8	22.5	2.81

kymographic and electrocardiographic records (Fig. 1, 2 and 3).

Several phenomena were observed in the ventricles. During the early period of atabrine injection the ventricles contracted with great irregularity which disappeared as the concentration of atabrine in the circulating blood was increased by virtue of the continuous infusion. As the infusion of atabrine was continued, the usual accompanying variations in the amplitude of the R wave became less pronounced despite the persistent auricular fibrillation (Fig. 2 and 3). It was also observed that intracardiac injection of atabrine failed to restore the fibrillating ventricle in 2 of the experiments.

The effect of atabrine was long-lasting. Attempts to reproduce auricular fibrillation after its arrest by atabrine were unsuccessful for approximately 2 hours in 2 experiments. In the remaining 3 experiments where auricular fibrillation was reproduced successfully, it was necessary to combine the application of mecholyl pledgets in the region of the S-A node with faradic stimulation of the right auricle for at least 30 seconds. The auricular fibrillation produced by this method was transient, rarely exceeding more than 20 seconds.

Discussion. Experimental evidence for another possible clinical application of atabrine has been brought out in the study of atabrine on the dog heart. The need for a drug in the treatment of auricular fibrillation which is as effective as digitalis or quinidine and which is not as toxic is obvious. It is noteworthy that atabrine, a drug which is efficacious in malaria therapy and which has proven itself to be virtually harmless by its long clinical record, should also control auricular fibrillation. After a survey of the literature, the only reference to atabrine and auricular fibrillation found was that made by Ganguli.[5] While studying the effects of atabrine on the electrocardiogram, in patients with malaria, he included one case which suffered from auricular fibrillation concomitant with malaria. The final electrocardiographic record did not reveal auricular fibrillation, but whether this may be attributed to atabrine or to the conventional forms of therapy cannot be stated with certainty from his article.

Obviously, any drug which reconverts auricular fibrillation into normal sinus rhythm must of necessity increase the refractory period of the "circus movements" in the auricular muscle and diminish the rate of conduction in these circuits.[4] No attempt was made in these experiments to analyze the mechanism by which atabrine restored regular sinus rhythm to auricular fibrillation. The auricular fibrillation produced in these experiments was of the vagal type, *viz.* increased vagal tone plus superimposed auricular excitation. It would be reasonable, therefore, to explain the action of atabrine in restoring regular sinus rhythm to this type of auricular fibrillation on the basis that atabrine paralyzes the vagal inhibitory fibers to the dog heart.[3] However, this explanation is not entirely adequate, for it is known that atabrine possesses such properties as decreasing the excitability of excised auricular tissue,[6] perfused hearts[7] and increasing the refractory period in skeletal muscle.[1]

In order to test the validity of whether the beneficial effect of atabrine in auricular fibrillation was merely due to its antivagal action, it was decided to inject eserine into an animal immediately after atabrine had restored regular sinus rhythm to the experimentally produced auricular fibrillation and observe whether it was possible to reproduce the fibrillation. It was found that auricular fibrillation could be produced with great difficulty and persisted for only 10 seconds. Furthermore, an exclusive antivagal effect is

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6 Suffolk and Berkshire, Earl of, *Quart. J. Exp. Physiol.*, 1939, **29**, 1.

7 Chin, K., *Japan J. Med. Sci., IV, Pharm.*, 1937, **10**, 162P.

opposed by the fact that it was impossible to reproduce auricular fibrillation in 2 experiments for a long period after its reconversion into normal sinus rhythm by atabrine despite the presence of a normal electrocardiogram.

While there is no experimental proof as yet, it is reasonable to assume from the evidence submitted that the mechanism of the action of atabrine on auricular fibrillation is similar to that of quinine and quinidine.

Summary. 1. Experimentally produced auricular fibrillation in the dog was successfully restored to normal sinus rhythm by the intravenous infusion of atabrine (average 2.17 mg per kg). 2. The mechanism by which atabrine might produce this effect is discussed. It is suggested that its action is similar to that of quinine or quinidine.

The authors are indebted to Dr. B. P. Babkin for suggesting this problem and for his advice and unfailing interest. To Dr. H. E. Hoff the authors are grateful for his valuable advice and criticism.

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15749 P

Effect of Penicillin on Growth and Toxin Production of Enterotoxigenic Staphylococci.*

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Little is known of the effect of penicillin on formation or activity of bacterial toxins. Ercoli, Lewis and Moench[1] demonstrated *in vitro* neutralization of diphtheria toxin-antitoxin mixtures; Boor and Miller[2,3] obtained protection *in vivo* against meningococcal and gonococcal endotoxin and Mason[4] demonstrated inhibition of plasma coagulation by enterotoxigenic staphylococci. Neter[5] failed to obtain neutralization of tetanus toxin and Blair, Carr and Buchman[6] found no inhibition of plasma coagulation and formation of hemolysin by staphylococci.

The present paper reports experiments on the effect of penicillin on formation of staphylococcal enterotoxin, hemolysins, lethal factor and dermonecrotoxin.

Tested by the tube dilution method,[7] the natural resistance of 15 enterotoxigenic strains of staphylococci was found to range from 0.05 units/ml to 500 units/ml of penicillin. Three enterotoxigenic (No. 147, 161, 196) and one nonenterotoxigenic (No. 43) strains used in the following experiments were naturally resistant to 500, 30, 100 and 0.1 units/ml of penicillin respectively. The resistance of strains 161 and 43 was further increased to 2000 and 10 units/ml respectively by growth in increasing penicillin concentrations. All strains were alpha hemolytic and strain 196 produced potent beta lysin.

Toxin production in the presence and absence of penicillin was tested in semisolid (0.7%) veal infusion agar and in liquid and semisolid media containing 1% Amigen,† 0.25% glucose, 1.2 μg/ml nicotinic acid, 0.05

* This work was supported in part by a grant from the National Canners Association.

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2 Boor, A. K., and Miller, C. P., *Science*, 1945, **102**, 427.

3 Miller, C. P., and Boor, A. K., PROC. SOC. EXP. BIOL. AND MED., 1946, **61**, 18.

4 Mason, H. C., *J. Immunol., Virus Res. and Exp. Chemother.*, 1945, **51**, 307.

5 Neter, E., *J. Infect. Dis.*, 1945, **76**, 20.

6 Blair, J. E., Carr, M., and Buchman, J., *J. Immunol., Virus Res. and Exp. Chemother.*, 1946, **52**, 281.

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† Pancreatic hydrolysate of casein free of vitamins and carbohydrate. Product of Mead, Johnson and Co.