methylnicotinamide in the urine. The evidence is definite that kynurenine can serve as a precursor of quinolinic acid and N^1-methylnicotinamide. 3. During 24 hours after injection of 1 mg of labeled DL-kynurenine, 6.86% was excreted as unchanged labeled kynurenine.

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1. Kallio, R. E., Berg, C. P., *J. Biol. Chem.*, 1949, v181, 333.
2. Wiss, O., Viollier, G., Müller, M., *Helv. Chim. Acta*, 1950, v33, 771.
3. Henderson, L. M., Koski, R. E., D'Angeli, F., *J. Biol. Chem.*, 1956, v223, 479.
4. Krehl, W. A., Bonner, D., Yanofsky, C., *J. Nutrition*, 1950, v41, 159.
5. Rosen, F., Huff, J. W., Perlzweig, W. A., *ibid.*, 1947, v33, 561.
6. Hankes, L. V., Segel, I. H., PROC. SOC. EXP. BIOL. AND MED., 1957, v94, 447.
7. Henderson, L. M., Hankes, L. V., *J. Biol. Chem.*, 1956, v222, 1069.
8. Dalgliesh, C. E., *Quarterly Reviews*, 1951, v5, 227.
9. De Castro, F. T., Price, J. M., Brown, R. R., *J. Am. Chem. Soc.*, 1956, v78, 2904.
10. De Castro, F. T., Brown, R. R., Price, J. M., *J. Biol. Chem.*, 1957, v228, 777.
11. Christman, D. R., *Brookhaven Nat. Lab. Quart. Rpt.*, 1956, vBNL 406 (S-30), 15.
12. Spacek, M., *Canadian Journal of Biochemistry and Physiology*, 1954, v32, 604.
13. Leonard, N. J., Boyd, N., *Jour. of Organic Chem.*, 1946, v11, 405.
14. Melander, L., Olsson, S., *Acta Chem. Scand.*, 1956, v10, 879.
15. Hankes, L. V., Henderson, L. M., Brickson, W. L., Elvehjem, C. A., *J. Biol. Chem.*, 1948, v174, 873.
16. Krehl, W. A., Strong, F. M., Elvehjem, C. A., *Ind. Eng. Chem.*, Anal. Ed., 1943, v15, 471.
17. Henderson, L. M., *J. Biol. Chem.*, 1949, v181, 677.
18. Carpenter, K. J., Kodicek, E., *Biochem. J.*, 1950, v46, 421.
19. Henderson, L. M., Hirsch, H. M., *J. Biol. Chem.*, 1949, v181, 667.
20. Henderson, L. M., Koski, R. E., D'Angeli, F., *ibid.*, 1955, v215, 369.
21. Wilzbach, L. K., *Symposium on Tritium in Tracer Applications, N. Y.*, N. Y., 1957.

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A Method for Production of Arrhythmias in the Isolated Rabbit Heart. (23808)

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Rosenblueth(1), Scherf(2), and Harris(3) have described methods for the experimental production of cardiac arrhythmias. These methods, performed on the intact dog *in situ*, are laborious and time consuming. The isolated heart offers a simple and inexpensive procedure for studying cardiac activity; therefore, a series of experiments were undertaken to determine whether it would be feasible to induce arrhythmias in the isolated rabbit's heart.

Materials and methods. Rabbit hearts were perfused by the Langendorff technic(4) with Locke-Ringer's solution prepared with double-distilled pyrogen-free water. The solution is oxygenated, maintained at 37.5° and perfused at 40 mm Hg. It has been found necessary to have both auricles distended by the perfusate, and this can be accomplished by tying off all vessels except the superior vena cava, which is partially ligated. Electrograms are recorded following an adjustment period of 15-20 minutes. Potential difference is measured by placing electrodes at various positions in the myocardium. In order to determine the type of arrhythmia produced, the number and position of electrodes are altered. When a constant pattern is obtained the

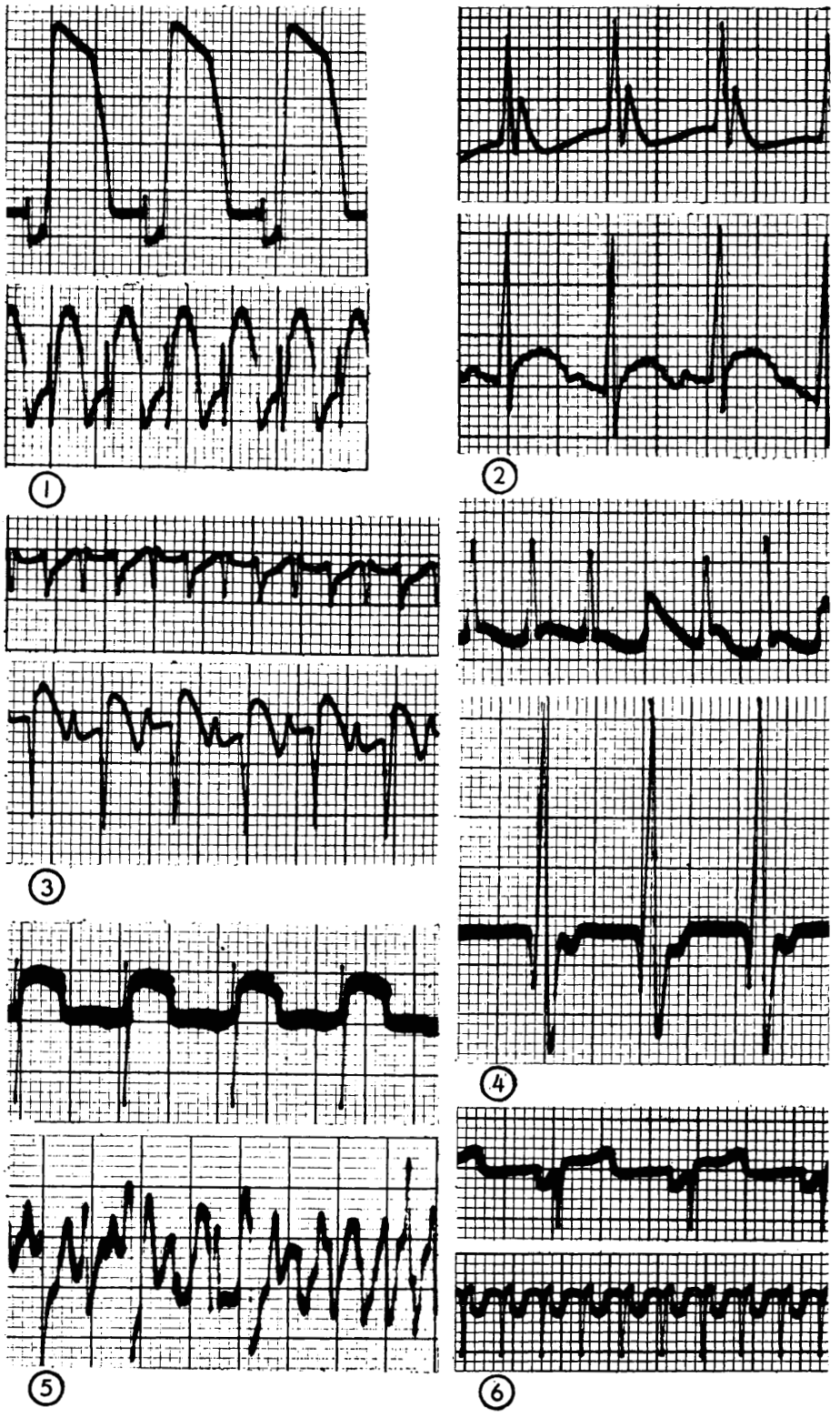
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FIG. 1. (Top) Normal electrogram (right auricle to left ventricle). Heart rate 116. (Bottom) Increased heart rate after electrical stimulation (tachycardia or flutter). Heart rate 236. Paper speed 25 mm/sec.

FIG. 2. (Top) Normal electrogram (right auricle to left ventricle). Heart rate 140. (Bottom) Right ventricle to left ventricle. Heart rate 140. Paper speed 25 mm/sec.

FIG. 3. (Top) Paroxysmal tachycardia instituted electrically. Right auricle to left auricle. Heart rate 216. (Bottom) Right auricle to left ventricle. Heart rate 216. Paper speed 25 mm /sec.

FIG. 4. (Top) A 2:1 auricular flutter instituted electrically. Right auricle to left auricle. Heart rate 498. (Bottom) Right ventricle to left ventricle. Heart rate 249. Paper speed 50 mm/sec.

FIG. 5. (Top) Normal electrogram (right auricle to left ventricle). Heart rate 138. (Bottom) Fibrillation pattern produced by electrical stimulation. Paper speed 25 mm/sec.

FIG. 6. (Top) Normal electrogram (right auricle to left ventricle). Heart rate 110. (Bottom) Increased heart rate after focal application of 0.05% aconitine nitrate. Heart rate 360.

cardiac rate is determined from the electrogram, and the heart is stimulated electrically. Electrical stimulation produces changes varying from paroxysmal tachycardia to atrial flutter and fibrillation. The same types of arrhythmia may also be produced by the topical application of 0.05% aconitine nitrate. An increased rate can be demonstrated by using two electrodes, embedding one in the right atrium and inserting the other in the tip of the left ventricle. The electrodes consist of two 12 mm lengths of enameled No. 30 copper wire which are soldered to Lead II electrodes of an electrocardiographic patient cable. After a normal electrogram is obtained, the right auricle is stimulated electrically for 5-10 seconds (5-10 volts, 50 pulses/second, pulse duration of 2-10 milliseconds, and pulse delay of 5 milliseconds). Fig. 1 shows a typical electrogram produced by this procedure. To differentiate between an atrial flutter and a paroxysmal tachycardia, 4 electrodes are placed in the myocardium. The 2 additional electrodes are soldered to an accessory shielded cable which is inserted into the input socket of the preamplifier on a Sanborn Twin-Viso Recorder. The potential differences are measured between the right and left auricles and the right and left ventricles. Fig. 2 shows a typical electrogram produced in this manner. Other leads may also be taken by varying the position of the electrodes. Fig. 3 and 4 respectively show the production of paroxysmal tachycardia and atrial flutter resulting from electrical stimulation. To demonstrate the induction of fibrillation, a normal electrogram is made by recording the potential difference between the right auricle and left ventricle. After the normal pattern is obtained the right and left auricles are rapidly stimulated alternately (140 volts, 50 pulses/second with a pulse duration of 2-10 milliseconds). Fig. 5 illustrates the fibrillation pattern produced in this manner. Focal application of 0.05% aconitine nitrate to the right auricle results in a tachycardia, atrial flutter, or fibrillation. Fig. 6 shows a tachycardia produced by this method.

Results. A total of 40 hearts was used to study the various arrhythmias discussed. Additional experiments were carried out to determine the duration of the induced arrhythmias. It was found that paroxysmal tachycardia and auricular flutter persisted for period varying 20 minutes to 6 hours, and at any time this could be reverted to a sinus rhythm by electrical stimulation. Further stimulation reestablished the arrhythmia. Once induced, a fibrillation would persist indefinitely.

Summary. A method has been presented for inducing experimental arrhythmias in the isolated rabbit heart. These vary from paroxysmal tachycardia to atrial flutter and fibrillation. Multiple leads from the myocardium are necessary in order to determine the type of arrhythmia produced. This method is inexpensive, rapid and the results are reproducible; therefore, we believe that this technic could be employed to advantage in screening eurhythmic agents.

1. Rosenblueth, A., Garcia, Ramos, *J. Arch. Inst. Cardiol. Mexico,* 1947, v17, 1.

2. Scherf, D., PROC. SOC. EXP. BIOL. AND MED., 1947, v64, 233.

3. Harris, A. S., *Circulation,* 1950, v1, 1318.

4. Langendorff, C., *Arch. ges. Physiol.,* 1895, v61, 292.

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