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Comparative Actions of Dextro- and Levo-Epinephrine on Human Heart.

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Shortly after the synthesis of epinephrine, studies were carried out on the comparative actions of the synthetic and the natural substances. Chemically the artificial base was identical with the natural substance in all respects except that it was optically inactive while natural epinephrine is levorotatory. Beberfeld[1] studied the comparative actions of racemic synthetic epinephrine and the levorotatory natural base in rabbits and concluded that they were exactly equivalent. Cushny[2] found in dogs that the natural epinephrine was twice as active on the blood pressure as the synthetic isomer and concluded that the dextrorotatory substance was devoid of action on the blood vessels. Since 1908 when the dextro-component became available, several observers have reported on the comparative activities of the isomers. Practically all agree that the d-isomer has a relatively weak action. The following ratios of activity have been reported in dogs: 1:12 to 1:15, by Cushny[3]; 1:15 by Abderhalden and Müller[4]; 1:15 to 1:20 by Tiffeneau[5]; and 1:30 to 1:40 by Fromherz.[6] Richaud,[7] however, concluded that levo-epinephrine was only slightly more active than the racemic form so that in therapy the synthetic substance should give approximately the same effect. His method, however, for estimating quantitative reactions is not entirely acceptable. In rabbits Launoy and Menguy[8] found a ratio of activity of 1:30, while in cats Tainter[9] reported a ratio of 1:20.

The method which has been used almost exclusively for the study of comparative actions of these isomers has been the pressor re-

1 Beberfeld, J., *Med. Klin.*, 1906, **2**, 1177.
2 Cushny, A. R., *J. Physiol.*, 1908, **37**, 130.
3 Cushny, A. R., *J. Physiol.*, 1909, **38**, 259.
4 Abderhalden, E., and Müller, F., *Z. f. Physiol. Chem.*, 1908, **58**, 185.
5 Tiffeneau, M., *Compt. Rend. de Acad. des Sciences*, 1915, **161**, 36.
6 Fromherz, K., *Deutsch. med. Woch.*, 1923, **49**, 814.
7 Richaud, A., *J. de Pharm. et Chem.*, 1922, **25**, 369.
8 Launoy, L., and Menguy, B., *Compt. Rend. Soc. de Biol.*, 1922, **87**, 1066.
9 Tainter, M. L., *J. Pharmacol. and Exp. Therap.*, 1930, **40**, 43.

sponse in experimental animals. Cushny[3] has pointed out that the comparative activities of optical isomers may not be the same on different organs. For example, he observed that in its peripheral action levo-hyoscyamin was 12 times as active as the dextro-isomer. He noted, however, that certain tissues prove exceptions to the general rule, as on the central nervous system d-hyoscyamin acted quite as strongly as the levorotatory substance.

The purpose of the present study was to determine whether the quantitative differences exhibited by the epinephrine isomers on the blood vessels of experimental animals apply to the human heart. It was previously demonstrated that natural epinephrine consistently abolished the cardiac standstill which may be induced in many human subjects by pressure on the right carotid sinus.[10] The standstill is abolished by the formation of secondary centers of impulse initiation in the ventricles. By applying varying doses of epinephrine intravenously it was observed that the rate of the ectopic pacemaker and the duration of the effect were proportional to the

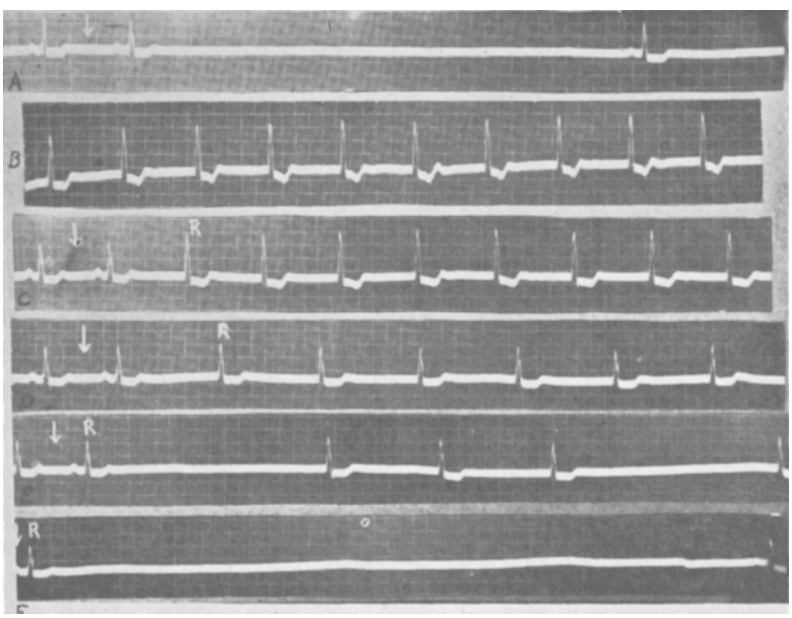

FIG. 1.

Strip A shows response to pressure on the right carotid sinus (arrow), cardiac standstill of 7.6 seconds. Lower strips show reaction to right carotid sinus pressure 2 minutes, 5 minutes, 10 minutes, 12 minutes and 15 minutes after the intravenous injection of 1/20 mg. of l-epinephrine.

[10] Nathanson, M. H., PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 967.

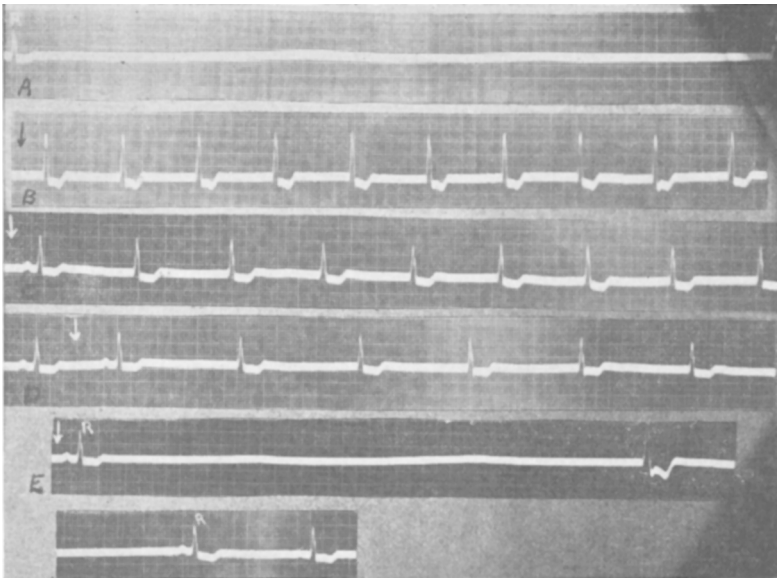

FIG. 2.

Strip A shows standstill of 11.8 seconds on right carotid sinus pressure. Lower strips show reaction to right carotid sinus pressure 2 minutes, 5 minutes, 10 minutes and 15 minutes after the intravenous injection of 1 mg. of d-epinephrine.

administered dose. Fig. 1 illustrates the response in one subject to 1/20 mg. of l-epinephrine intravenously showing a maximum rate of the ventricular pacemaker of 60, and the duration of effect of 15 minutes. A dose of 1/5 mg. produces a more rapid ventricular rate of longer duration while the response to 1/50 mg. is a slow ventricular rhythm of a shorter duration, 8 to 10 minutes. Repeated administration of these doses gave consistent responses. The reaction to d-epinephrine was studied on 3 occasions.* In each experiment 1 mg. of d-epinephrine produced a reaction practically identical in intensity and duration with that obtained by 1/20 mg. of l-epinephrine, thus giving a ratio of activity of 1:20. These experiments indicate that the human ventricle discriminates between the epinephrine isomers in the same manner as has been previously demonstrated for the blood vessels of experimental animals.

The pressor reactions to both isomers showed the same quantitative differences. In each case the blood pressures were between 140 and 150 systolic and 80 to 90 diastolic before the injection. After

* The d-epinephrine was supplied by the H. A. Metz Laboratories as the bitartrate. For purposes of comparison with the l-epinephrine, which was in the form of hydrochloride, the doses are expressed in terms of epinephrine base.

the injection of 1/20 mg. of l-epinephrine the pressure rose to 198 systolic and 110 diastolic. The administration of 1 mg. of d-epinephrine produced a rise in systolic pressure to 190 and in the diastolic to 110. The blood pressures returned to the original level within 3 minutes with both substances. With both isomers the duration of the cardiac effect was 5 times that of the pressor reaction.

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Iodine Content of Human Skim Milk from Goitrous and Non-goitrous Regions.

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Published figures for the iodine content of cow's and women's milk are not consistent. The foreign investigators[1] report for cow's milk, 1γ-3γ% and for human milk after the fifth lactation day 2γ-4γ%. American investigators[2] find that the percentage in cow's skim milk, calculated on the dry basis, may vary between 14.0γ and 130.0γ%.

This investigation includes a study of the iodine content of the milk from mothers in Detroit, a goitrous region, and from mothers in Boston, a non-goitrous region. The mothers were normal and showed no signs of thyroid hyperplasia. The value of iodine was determined in the milk of mothers at varying intervals during the mature lactation period. The calcium and inorganic soluble phosphates were also determined and compared with the fluctuations found for iodine.

The milk was obtained through the courtesy of the Detroit Mother's Milk Bureau and The Directory for Mother's Milk, Boston. Nine cases were studied from the former and 10 cases from the latter.

Micro methods were used for the determination of calcium, in-

[1] Maurer, E., and Diez, S., *Munch. Med. Woch.*, 1926, **73**, 17; von Fellenberg, T., *Ergebn. Physiol.*, 1926, **25**, 176; Maurer, E., and Ducrue, H., *Munch. Med. Woch.*, 1928, **75**, 249.

[2] McClendon, F., Remington, R. C., and von Kolnitz, H., *J. Am. Chem. Soc.*, 1930, **52**, 541; 1931, **53**, 1245.