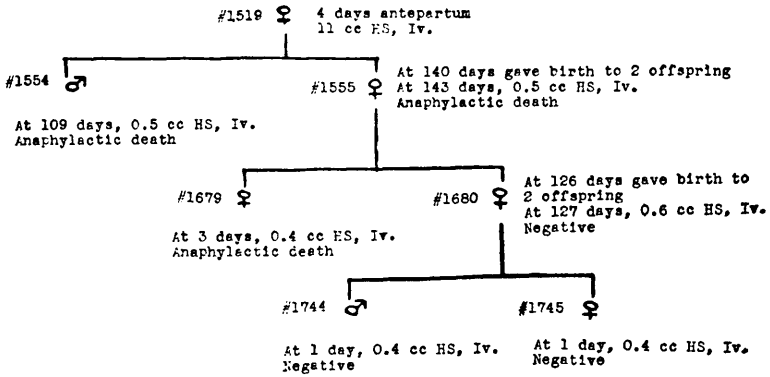

spring, the third generation. This passive sensitization wears off in the third generation, before the birth of the fourth generation.

Thus the transmission of hypersensitiveness here is *congenital* and either active or passive in nature. When it is passive it can be transmitted only to the succeeding generation, when it is active it may be transmitted through a second generation to a third generation.

This mechanism, we believe, is intimately associated with the problem of the sensitization of the human fetus.[3]

4457

Effect of Calcium and Potassium on Action of Ephedrine.

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The action of ephedrine on the isolated heart was studied by several investigators, among them Chen and Meek,[1] Barlow and Sollman,[2] and Da Costa.[3] The latter also made observations on the influence of calcium and potassium upon the paralyzing action of ephedrine on the heart. It seemed, nevertheless, desirable to repeat these experiments especially for the purpose of using them as a basis of comparison with the effects of ions on the action of this substance. We, therefore, carried out experiments with ephedrine and different amounts of calcium and potassium, and also when either one or

[3] Katner, B., *Am. J. Dis. Child.*, 1928, xxxvi, 277.

[1] Chen and Meek, *J. Phar. and Exp. Ther.*, 1926, xxviii, 31.

[2] Barlow and Sollman, *J. Phar. and Exp. Ther.*, 1927, xxx, 21.

[3] Da Costa, S. F. G., *Comp. rend. Soc. de biol.*, 1927, xcvi, 1332.

both ions were omitted from the solution containing the substance. The experiments were conducted on the isolated frog heart which was perfused by a method that is a modification of the one previously used by the senior author and his collaborators.[4] As it will be published separately by one of us (V), its description is not included in the present report. The results which we obtained with different concentrations of ephedrine in normal Ringer indicate that small amounts, 1-1,000,000 to 1-1,100,000, sometimes increased moderately the force of the contractions. Stronger concentrations, 1-10,000 and especially 1-5,000, greatly decreased the amplitude and to a smaller extent also the rate. Recovery occurred in all cases, neither the duration of the exposure to ephedrine nor the amount of depression which it produced exerting any injurious effect. We noticed, on the contrary, that the contractions were stronger in the after period than in the fore period. By varying the calcium content the following results were obtained with ephedrine. Solutions of 1-100,000 and an excess amount of calcium (0.096%) produced no effect or slight stimulation, the behavior of the heart being the same as when perfused with normal Ringer containing the same amount of ephedrine. The action of larger amounts of ephedrine depended upon the concentration of calcium. When the latter was increased to 8 times the normal amount (0.096%), the depression produced by 1-5,000 ephedrine was abolished. Increase of calcium to 4 times the quantity in normal Ringer still antagonized the action of this amount of ephedrine, but this was not observed when the concentration of calcium was doubled, its action being the same as when perfused with normal Ringer.

The activity of ephedrine is also modified by reducing the amount of calcium. Stronger solutions (1-5,000) of ephedrine in 0.006% calcium produced much greater depression than the same concentration in normal Ringer. But if the amount of calcium was reduced to 0.003% little or no change was produced by ephedrine. In all experiments with deficient calcium initial stimulation, lasting about 20 seconds, was observed when the heart was perfused with ephedrine, and this was much greater when calcium as well as potassium was reduced to one fourth the normal amount. By removing both calcium and potassium from the solution the action of ephedrine was still more increased, the force of the contractions being augmented several times in one experiment while in another in which the heart was brought to a standstill, contractions appeared promptly when perfusion with 1-5,000 ephedrine was begun and

[4] Salant and Livingston, *Am. J. Physiol.*, 1916, xli, 21.

lasted several minutes. It was observed, however, that a repetition of the perfusion with ephedrine was without effect. Weak solutions, 1-1,000,000, also stimulated the heart but this was transitory, and was appreciably less than after perfusion with the stronger solutions. But omission of calcium, which caused the usual effect, produced no change upon adding ephedrine, the heart remaining at a standstill. The results obtained when ephedrine and different amounts of potassium were perfused through the heart were not constant. Depression was produced by a strong solution of ephedrine, the amplitude was moderately decreased and the heart rate was also slower, but it was less affected than the force of the contractions. In some experiments the same amount of ephedrine arrested the heart for a brief period after it was perfused for 20 to 30 seconds with such a solution containing 4 and 8 times the amount of potassium in normal Ringer. The effect in others was marked by pronounced arrhythmia, heart block, and group contractions which occurred when 4 times normal potassium and ephedrine were perfused. It was also observed in this case that heart action was greatly stimulated when this solution was followed by normal Ringer without ephedrine, no such after effect being noticed when heart action was regular during perfusion with such a solution. Experiments were also performed with ephedrine in Ringer solution containing 0.035% or one fourth normal potassium. Ephedrine in this case slowed the heart considerably and greatly decreased the force of the contraction in one experiment. However, this was observed only after the second perfusion, the amplitude after the first perfusion being appreciably increased.

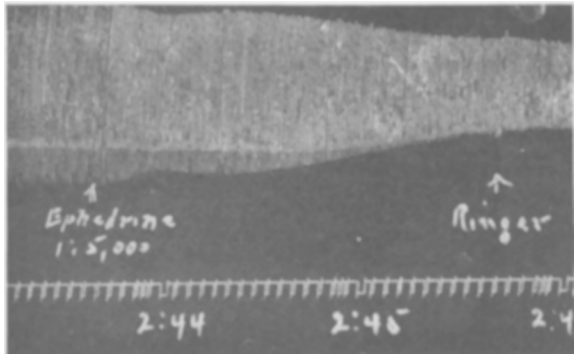
These results led to the further inquiry into the action of ephedrine in excess potassium and calcium. Ephedrine improved heart action also in this case. The contractions, though slower than normal, became regular after 1 or 2 minutes. The beneficial action was further indicated when the same Ringer solution without ephedrine was perfused. Complete heart block alternating with groups of 5 or more contractions occurred and persisted during the perfusion.

It may be added that powdered as well as crystalline ephedrine was used in these experiments. It was sometimes found that the latter was less effective.

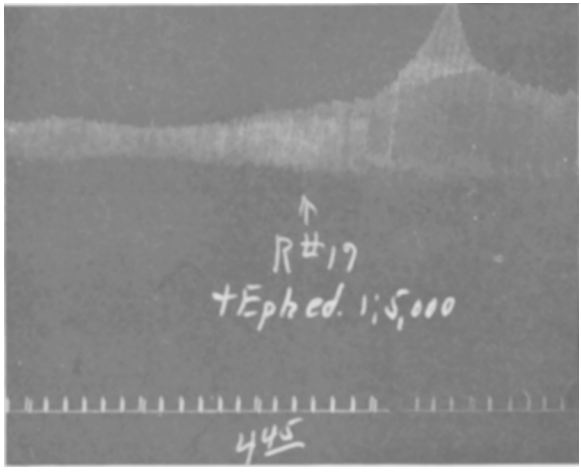
Summary. 1. Small amounts of ephedrine in normal Ringer either increase cardiac activity moderately or are without effect, but a concentration of 1-5,000 always depresses the heart.

2. The depression produced by ephedrine is antagonized by adding sufficient amounts of calcium and aided by reducing the cal-

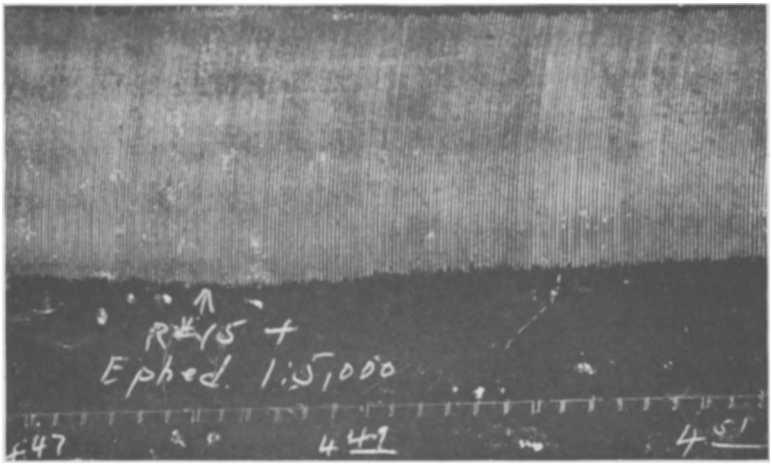
FIG. 1.



A. Ephedrine in normal Ringer.

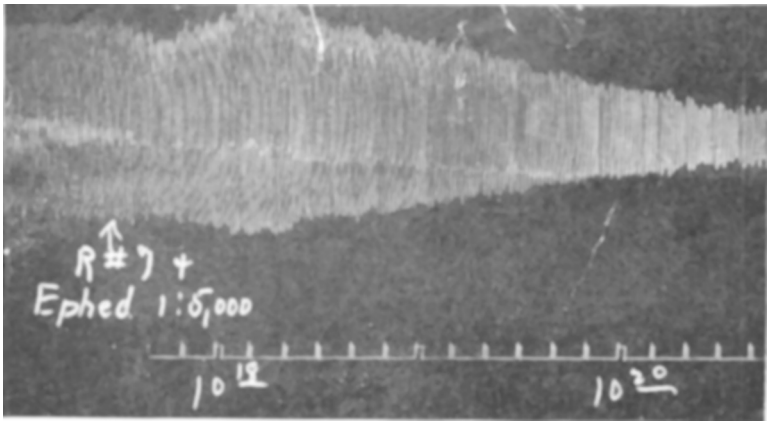


B. Ephedrine in Ringer minus calcium and potassium.

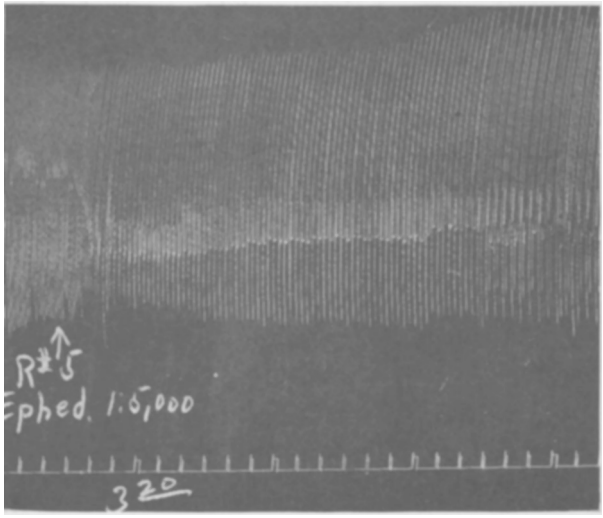


C. Ephedrine in Ringer containing 8 times the amount (0.096%) of calcium in normal Ringer.

FIG. 2.



A. Ephedrine in Ringer containing 0.006% (half normal) calcium.



B. Ephedrine in Ringer containing 0.048% (4 times normal) potassium.

cium content to about 50%. In still smaller amounts of calcium ephedrine is inactive.

3. Ephedrine stimulates the heart when both ions are omitted.

4. Ephedrine in excess potassium depresses the heart but this is much less than in deficient calcium.