FIG. 1.
Microphotograph of parietal thrombo-endocarditis and mural thrombosis in femoral artery produced in rabbit at the site of local preparatory inoculation subsequent to intravenous injection of "agar washings" meningococcus filtrate. × 95.

was seen in 5 animals, valvulitis was noted only once. The latter finding must, therefore, be considered with reservation.

Shwartzman Phenomenon in the Femoral Artery. Again, the meningococcus filtrate in a dose of 0.03 cc of a dilution of 1:30 produced the same negligible primary tissue reaction as in the heart. Three rabbits were prepared peri-arterially. Three other rabbits received the preparatory injection into the lumen of the artery. All rabbits were injected intravenously 24 hours later with the same filtrate as above (1 cc per kg of filtrate, diluted 1:30). In each instance the reaction at the site of preparation was characterized by an outstanding necrotizing and hemorrhagic lesion. Overwhelming leucocytic infiltration and frequent luminal thrombosis were consistently found in both series (Fig. 1).

In 3 out of 4 animals the phenomenon was successfully elicited simultaneously in the heart and femoral artery.

Summary. To sum up, the Shwartzman phenomenon of local tissue reactivity was successfully produced in the heart and blood vessels by the use of "agar washings" filtrates of meningococcus. The hemorrhagic and necrotizing feature of the reaction together with altered vascular response at the sites of preparation were consistent findings.

13231 P

Smooth Muscle Effects of Carnosine.

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(Introduced by V. du Vigneaud.)

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Koinaroff[1] reported that carnosine, B-alanyl-l-histidine, produced a marked increase in the tonus of isolated rabbit intestine. McClintock and Hines[2] confirmed this observation and also noted that

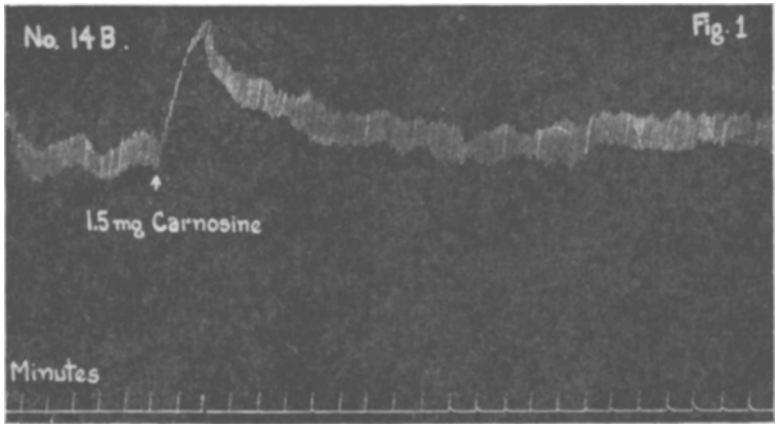
[1] Koinaroff, S. A., *Chem. Zentralblt.*, 1922, 636.

[2] McClintock, J. T., and Hines, H. M., PROC. SOC. EXP. BIOL. AND MED., 1924-25, **22**, 515.

carnosine caused a similar increase in tonus and rhythmical contractions of the isolated guinea pig uterus. Contrary to this view is the work of McClosky, *et al.*,[3] who were unable to substantiate the reported oxytocic effect of carnosine on uterine strips.

In the light of the somewhat conflicting work on uterine strips, we thought it would be worthwhile to reinvestigate the smooth muscle action of carnosine.* In the present work, isolated monkey† intestine was used. Oxygenated Tyrode's solution served as a physiological bath for these experiments. The temperature was kept at 37.5°C. Forty-eight experiments using various doses of carnosine were performed. Fig. 1 illustrates the typical effect as noted with 1.5 mg of this drug in a 100 cc bath.

For a long time we have been interested in the fact that morphine causes a relaxation of the isolated intestine in various animals, but markedly stimulates the tone of the intact intestine. While many workers, Dreyer,[4] Gruber, *et al.*,[5] and others have reported a stimulating effect of morphine on isolated intestine, we have never



This illustrates the marked stimulant effect of carnosine on isolated monkey intestine. Time trace, minutes. Kymograph speed, 6 mm per minute. Bath, 100 cc.

3 McClosky, W. T., Miller, L. C., Hunt, Madison, and du Vigneaud, Vincent, PROC. SOC. EXP. BIOL. AND MED., 1937-38, **37**, 60.

* The carnosine used in this study was prepared and kindly furnished by Dr. Vincent du Vigneaud.

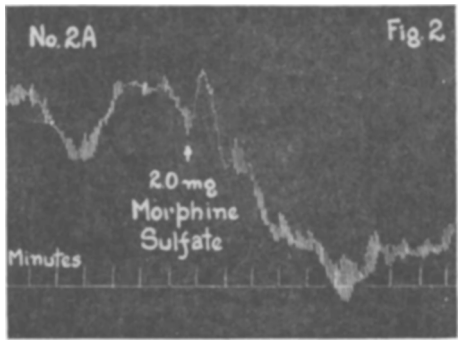
† Furnished by Dr. A. I. Folsom, Department of Urology, Baylor University Medical School. These were castrate female monkeys who had received repeated doses of testosterone propionate. Expert opinion given indicates that such treatment would not alter the activity of the intestine.

4 Dreyer, N. B., *Arch. Internat. de Pharmacol. et de Therap.*, 1933, **45**, 397.

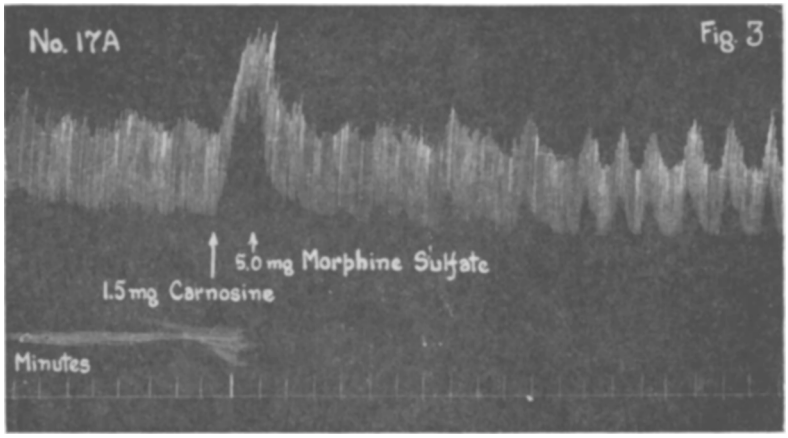
5 Gruber, C. M., Brundage, J. T., De Note, Anthony, and Heiligman, Raymond, *J. Exp. Pharm. and Therap.*, 1935, **55**, 430.

consistently obtained such results. Rather, it has been our belief that in isolated tissue some necessary substance was lacking which prevented morphine from giving a typical response such as is seen in the intact animal. To test this hypothesis, 25 experiments were done on the isolated monkey intestine using morphine alone. Fig. 2 exemplifies the usual response; *i. e.*, relaxation. When carnosine was given previously, however, a large dose of morphine did not cause relaxation (Fig. 3).

Since the tissues available were not too extensive (10 monkeys), we hesitate to report a few suggestive results which seem to indicate that carnosine may have a cholinergic-like effect on the isolated intestine.



This tracing demonstrates the typical effect of morphine on isolated monkey intestine. Note the marked relaxation of intestinal tonus. Time trace, minutes. Kymograph speed, 6 mm per minute. Bath, 100 cc.



This tracing illustrates that morphine does not cause relaxation of isolated monkey intestine; that is, after carnosine has been given previously. Time trace, minutes. Kymograph speed, 6 mm per minute. Bath, 100 cc.

We feel that these results indicate that carnosine is a stimulant of isolated intestine and that it prevents the morphine relaxation effect on such tissues. Since morphine always increases the tone of the intact intestine, it may be that "carnosine lack" is the cause of the failure of such a response in isolated material. Studies to correlate the disappearance of carnosine with the effect of morphine on the isolated intestine are planned.

13232 P

Relation of Gastric Acidity to Alveolar Bone Resorption.

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The absorption of calcium occurs chiefly from the upper part of the small intestine, the reaction of whose contents has been shown[1] normally to be acid. Irving and Ferguson[2] found the absorption of calcium to be facilitated when solutions of calcium chloride, deposited directly in the intestine of dogs, were buffered so as to maintain an acid reaction. There is a direct relationship between pH of the intestinal contents and gastric free acidity[3] and with advancing age there is a reduction in gastric acidity of both sexes.[4] Clinical experience[5] indicates that periclasia, one feature of which is alveolar bone resorption, is a condition which rarely occurs before age 20 but increases markedly in incidence after age 30. The coincidence of approximately equal age distributions of cases of physiological hypochlorhydria, periclasia and senile osteoporosis suggests that some cases of alveolar bone resorption are due to deficient calcium absorption consequent upon the secretion of an amount of hydrochloric acid by the stomach insufficient to maintain the normal acidity of the intestinal contents.

Seventy-nine individuals were subjected to gastric analyses, using

[1] Myers, F. J., and McClendon, J. F., *J. Biol. Chem.*, 1920, **41**, 187.

[2] Irving, L., and Ferguson, J., PROC. SOC. EXP. BIOL. AND MED., 1924-25, **22**, 527.

[3] Kearney, R. W., Comfort, M. W., and Osterberg, A. E., *J. Clin. Invest.*, 1941, **20**, 221.

[4] Vanzant, F., Alvarez, W. D., Eusterman, G. B., and Dunn, H. L., *Arch. Int. Med.*, 1932, **49**, 345.

[5] Brekhus, P. J., *J. Am. Dent. Assn.*, 1929, **16**, 2237.