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A Vaso-Depressor Phenomenon Caused by Some Cholecystokinin Preparations.

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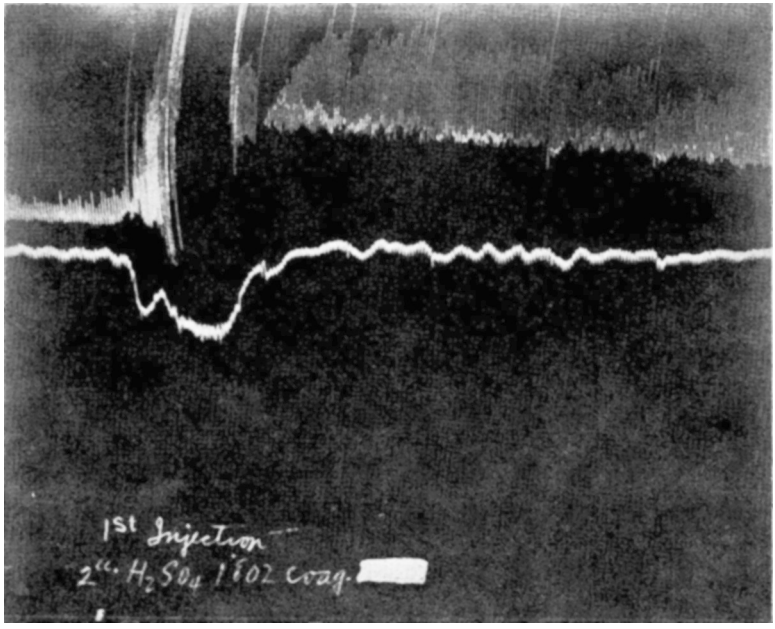
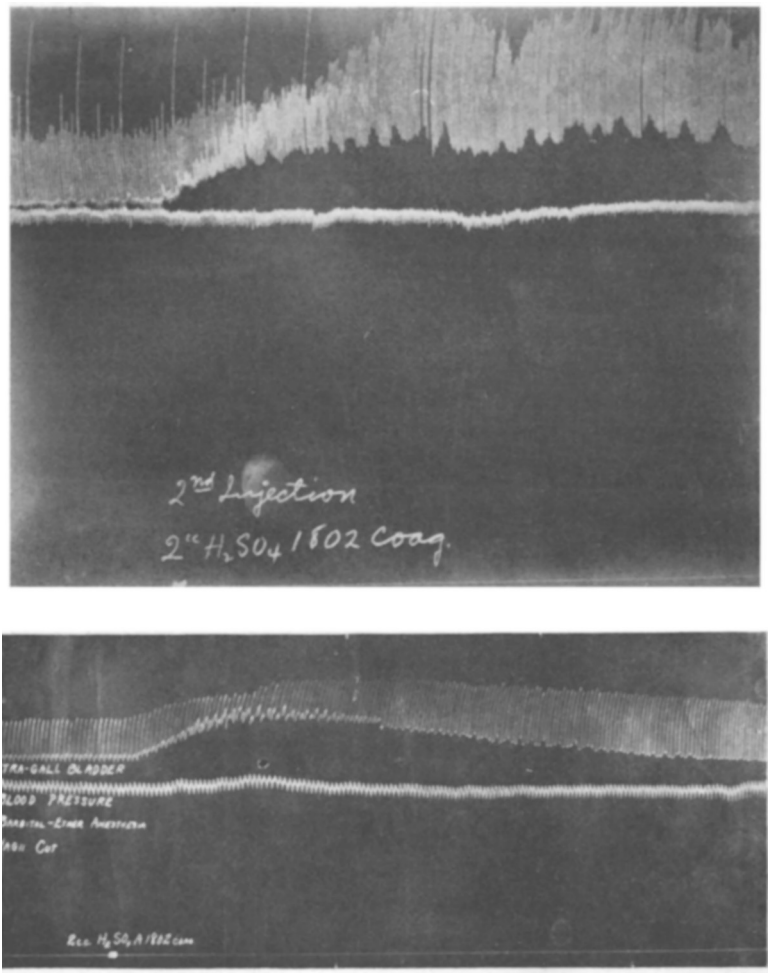
Throughout our work on the purification of cholecystokinin, we have not infrequently observed that certain preparations on their first injection into some dogs under barbital anesthesia cause marked contraction of the gall-bladder, followed by a slow fall in blood pressure (30-60 mm. Hg.) with a gradual return to normal, and a stimulation of respiration (which does not always occur) that appears soon after the blood pressure begins to fall. (The contraction of the gall-bladder persists from 10 to 20 minutes after the blood pressure and respiration have returned to normal. A second injection of the same material some 10 or 20 minutes later causes the gall-bladder to contract, but has no effect on the blood pressure and respiration. Apparently some rapid compensatory change or readjustment has occurred in the animal.

Two possible explanations of this phenomenon have occurred to us: one, that a rapid and violent contraction of the gall-bladder stimulates vagus endings and leads to the change in blood pressure and



respiration; the other, that there is some toxic element in the preparation to which the dog rapidly immunizes or adjusts itself. This latter possibility seems reasonable since our records show that we have only observed this phenomenon when the cholecystokinin was prepared from hog's intestines, and it has not occurred when dog's intestines were used. The dog's intestines used are very fresh, but we have to wait some 15 or 20 minutes after the death of the hog before we can get the intestine. Our hog material has never been as pure as our dog material.



Tracing 1 shows the response to the first injection of our preparation. In some dogs the fall in pressure occurs later and more slowly and the rise more slowly. Tracing 2 shows the response to the second injection approximately 20 minutes later in the same dog. Tracing 3 shows the response in a dog with the vagi cut.

The first hypothesis was tested as follows: we used a preparation that was known to produce the above phenomenon in some dogs. We made injections under barbital anesthesia in 20 dogs with vagi cut and in 10 without the vagi cut. The phenomenon occurred in 5 of the 10 dogs with the vagi intact. In the 20 dogs with the vagi cut, the phenomenon occurred in 4 cases. In one, the fall of blood pressure amounted to only 20 mm. Hg., but was a typical slow fall and return to normal. In another the fall was marked, 80 mm. Hg., and in the other the fall was 50 mm. Hg. If we had not used 20 dogs, we would not have observed the last 3 cases, and would probably have been led to an erroneous conclusion. These results show that this phenomenon will occur after the vagi have been cut. We have also observed a fall occur in one dog after atropine.

Our results indicate that this phenomenon is due to some toxic substance against which the body rapidly immunizes or adjusts itself.

Abel and Geiling[1] report that some 6% of dogs have a natural immunity to "peptone" and that dogs that survive "peptone" shock are immune to repeated injections. The causative agent of the phenomenon we have observed is precipitated by NaCl from acid solution and by 5% trichloracetic acid, and is not coagulated nor denatured by heating at boiling temperature for 30 minutes.

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Effect of Histamine on Gall-Bladder Evacuation.

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It has been shown in a previous article that 0.4% HCl in the duodenum causes the gall-bladder to contract on the basis of a humoral mechanism.[1] It has also been shown that histamine when injected intravenously causes the gall-bladder to contract, but the contraction is a mirror-image of the fall in blood pressure which led us to believe that the contraction was due to the fall in blood pressure.

It occurred to us that since it is well known that histamine subcutaneously causes gastric juice to be formed, such an injection

[1] Abel and Geiling, *J. Phar. Exp. Therap.*, 1924, xxiii, 1.

[1] Ivy, A. C., and Oldberg, Eric, *Am. J. Physiol.*, 1928, lxxxvi, 599.