The accentuated sound usually became audible as a presystolic gallop rhythm. It is related to the increased intraäuricular pressure following ventricular infarction and heart failure.

3. *Third Heart Sound.* A third sound, occurring in early diastole, was present in 47% of cases of infarction and in only 12% of normal subjects. It was definitely accentuated in 8%, forming an audible protodiastolic gallop rhythm. The third sound is related to the early diastolic filling of the ventricles when the inrushing blood from the auricles impinges on the ventricular wall. A decreased ventricular tonus and increased intraäuricular pressure which occur in infarction favor the production of a third sound of increased intensity.

In 6% of the cases there was a superimposition of the normal or accentuated auricular and third sound forming a clinically audible summation gallop rhythm.

Summary. In myocardial infarction due to acute coronary occlusion the first sound is usually diminished in amplitude both absolutely and relatively to the second sound, and is of low pitch owing to the small amplitude of the high frequency component. There is an increased incidence of auricular and third sounds. The accentuation of these sounds by increased intraäuricular pressure and decreased ventricular tonus often results in gallop rhythm.

12069

Liver Histamine During Peptone Shock in Dogs.

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Dragstedt and Mead[1] reported that the vascular shock produced by the intravenous injection of proteose solutions into dogs is accompanied by the appearance in the blood and thoracic duct lymph of a vasodepressor substance which was tentatively identified as histamine. Dragstedt, Mead and Eyer[2] presented additional evidence that the vasodepressor substance was histamine. They likewise presented indirect evidence that the amount of histamine liberated from the fixed tissues is adequate to account for the degree of shock

[1] Dragstedt and Mead, *J. Pharm. and Exp. Ther.*, 1937, **59**, 429.

[2] Dragstedt, Mead and Eyer, *J. Pharm. and Exp. Ther.*, 1938, **63**, 400.

and concluded that "the vascular shock produced by the intravenous injection of peptone solutions (which contain proteose) into dogs is due to the liberation of histamine from the tissues into the circulating blood." Feldberg and O'Connor[3] have reported that perfusing guinea pigs' lungs with peptone solution leads to the appearance of histamine in the perfusate and have concluded that peptone causes a type of cell injury with resultant liberation of histamine. Their observations on guinea pig lungs have been confirmed in this laboratory.

There is a certain amount of circumstantial evidence indicating that the liver is the major tissue concerned in the reaction in the dog. For example, the coagulation defect in peptone shock is commonly considered as an hepatic reaction.[4] The experiments here reported were planned as a test of the histamine liberation theory, and the liver was chosen as the tissue to be studied. Biopsy specimens of liver tissue were obtained before and after the injection of peptone solutions, analyzed for their histamine content, and the changes in liver histamine correlated with the degree of the reaction produced as indicated by the blood pressure responses.

Method. Dogs were used. All animals were anesthetized with ether or sodium barbital, and records made of the carotid pressure. A 10% solution of Bacto-Protone (Difco) was used; all solutions were freshly prepared, acidified, shaken with permutit, and then filtered and neutralized prior to use. This procedure removes more or less completely the vasodepressor constituents of the solution so that the blood pressure fall obtained measures the degree of the "peptone shock" without any confusion from the direct effect obtained from many peptone solutions. A dose of 2 cc per kilo was injected rapidly via the femoral vein.

It has been noted previously[1] that there is no direct correlation between the dose of peptone injected and the degree of effect produced. The dose here used (2cc per kilo) has been found to produce reactions in various animals that range from insignificant changes in the blood pressure to a rapidly fatal shock. Consequently, while it is not necessary to vary the dose of peptone in order to obtain reactions of varying degrees for study, it is obviously important to determine in each experiment the degree of the reaction experienced. The degree of the resulting reaction was determined from the blood pressure record and expressed by the following arbitrary schema: ++++ = shock fatal within 30 minutes, +++ = severe shock

[3] Feldberg and O'Connor, *J. Physiol.*, 1937, **90**, 288.

[4] Wöhlisch, *Ergebn. Physiol.*, 1929, **28**, 443.

with blood pressure still at shock level 30 minutes after injection, ++A = shock with blood pressure at shock level for 20 minutes but with some recovery before 30 minutes, ++B = shock with blood pressure at shock level for 10 minutes but with some recovery before 20 minutes, ++C = shock with blood pressure falling to shock level but with recovery before 10 minutes, + = mild reaction with a slight temporary fall of blood pressure. The abdomen was opened, and just prior to and again a few minutes after the injection of peptone a 2 to 4 g portion of liver was excised. Care was taken to secure hemostasis. These liver samples were analyzed for their histamine content by the method of Best.[5] The assays were made on an etherized, atropinized cat against known dilutions of histamine acid phosphate. At the conclusion of the experiment the dog's liver was removed and weighed, after permitting the freely draining blood to escape. Calculations of the total liver histamine were made on the assumption that there is an even distribution of histamine throughout the liver. Several control experiments indicate that this

TABLE I.
Liver Histamine During Peptone Shock in Dogs.

1	2	3	4	5	6	7	8	9	10
1	13.4	394	+	37.5	15.0	50.0	19.7	—	—
2	10.0	445	+	75.0	33.4	75.0	33.4	—	—
3	10.7	252	+	35.0	8.8	35.0	8.8	—	—
4	6.8	332	+	150.0	49.8	150.0	49.8	—	—
5	9.3	305	++C	120.0	36.6	120.0	36.6	—	—
6	8.0	230	++C	75.0	17.2	48.0	11.0	6.2	0.77
7	10.0	260	++C	150.0	39.0	105.0	27.3	11.7	1.1
8	15.2	580	++B	150.0	87.0	105.0	61.0	26.0	1.7
9	5.5	175	++A	150.0	26.0	67.0	12.0	14.0	2.5
10	6.1	223	+++	150.0	33.5	37.5	8.4	25.1	4.1
11	6.1	287	+++	135.0	38.0	60.0	17.0	21.0	3.5
12	6.4	270	+++	170.0	46.0	75.0	20.0	26.0	4.0
13	8.3	378	+++	135.0	51.0	50.0	19.0	32.0	3.8
14	10.7	441	++++	105.0	46.3	75.0	33.0	13.3	1.2
15	6.4	273	++++	165.0	45.0	52.5	14.0	31.0	4.8

Column 1—Exp. No.
" 2—Wt of dog (kg).
" 3—Wt of liver (g).
" 4—Degree of shock—see text.
" 5—Pre-shock liver histamine equivalent in μg of histamine acid phosphate per g.
" 6—Total pre-shock histamine equivalent in mg of histamine acid phosphate.
" 7—Post-shock liver histamine equivalent in μg histamine acid phosphate per g.
" 8—Total post-shock liver histamine equivalent in mg of histamine acid phosphate.
" 9—Total amt of histamine liberated from liver in mg.
" 10— " " " liberated histamine in mg per kilo of dog.

[5] Best, *J. Physiol.*, 1929, **67**, 256.

is a valid assumption. The results are shown in Table I, in which, for the sake of convenience, the experiments have been listed in the order of increasing severity of the shock reactions obtained.

Discussion. It will be noted that in every instance of a severe reaction there was a marked reduction in the liver histamine, while there was no reduction in the animals that had mild reactions. In one of these (Exp. 1) there appeared to be an increase in the liver histamine. Whether this is a real increase or merely an assay error is not possible to say. Tarras-Wahlberg[6] has reported that various procedures such as asphyxia result in an increase in the lung histamine of cats and rabbits. While his findings cannot properly be applied to the present experiments, they show that various non-shocking experimental procedures tend to result in an increase rather than a decrease in the tissue histamine. In the present experiments, the substantial reductions in liver histamine, amounting in 6 instances to more than 50% of the initial value, are considerably beyond any assay error. The histamine lost by the liver, calculated in terms of the body weight of the animal (Column 10 in the table), ranges from 0.77 to 4.8 mg of histamine acid phosphate per kilo. With the single exception of Experiment 14, the degree of the shock reaction is extremely well correlated with the amount of histamine lost by the liver; and even in this experiment the reaction is not beyond what can be accounted for by a corresponding dose of histamine.[7] It is highly probable that proteoses lead to the liberation of histamine from other tissues than the liver, but the results here reported would indicate that such other sources are relatively insignificant in the pathogenesis of the systemic reaction since the quantity liberated by the liver is substantially adequate to account for the degree of shock in every case. For the same reason it can be stated that tissue constituents other than histamine, if they are concerned at all, would appear to be of minor significance in the reaction. This statement applies, of course, only to the vascular reaction. The coagulation defect in peptone shock has been demonstrated to be due to the liberation of heparin.[8, 9]

Conclusion. Peptone shock in the dog is accompanied by a reduction in the liver histamine which is roughly parallel to the degree of the shock reaction. The amount of histamine liberated from the liver is substantially adequate to account for the degree of shock as determined by the systemic blood pressure.

[6] Tarras-Wahlberg, *Skand. Arch. f. Physiol.*, 1936, **73**, Supp. 1.

[7] Dragstedt and Mead, *J. Pharm. and Exp. Ther.*, 1936, **57**, 419.

[8] Quick, *Am. J. Physiol.*, 1936, **116**, 535.

[9] Waters, Markowitz and Jacques, *Science*, 1938, **87**, 582.