

Alterations in the Blood Histamine in Shock.

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Within the last decade much experimental data has accumulated on the subject of shock, and the explanation of its mechanism has been greatly clarified. There is still considerable controversy, however, about the actual factors responsible for the production of this syndrome. A discussion of the prevalent theories cannot be undertaken here for reasons of space but excellent reviews are available. (Moon.¹)

In an effort to investigate the relationship of histamine to various clinical conditions, the total blood histamine of a series of normal individuals was determined, using the method of Barsoum and Gaddum² as modified by Code.³ Since the production of reactive hyperemia by prolonged stasis of the circulation has been demonstrated to increase the blood histamine (Barsoum and Smirk⁴), specimens were obtained observing precautions against stasis. In a series of 50 controls the average figure was found to be 0.04 γ /cc (as base) with variation of from 0.025 to 0.08 γ /cc. These figures agree in general with those of Haworth and MacDonald,⁵ although they found a variation from 0.018 γ /cc to 0.078 γ /cc. In repeated examinations of the blood of the same individual from time to time over a period of months, it has been found that the blood histamine remains at a fairly constant level. For example, in a patient whose first sample contained 0.07 γ /cc subsequent samples at intervals of 2 days contained 0.07, 0.065 and 0.07 γ /cc. Three more at weekly intervals and a later one taken 2 months after the initial examination all gave values of 0.07 γ /cc. In several of the patients, one with an initial blood histamine value of 0.05 γ /cc and another with 0.04 γ /cc similar results were obtained. In a series of 150 patients with various conditions, 19 cases presenting shock varying from a mild form to severe collapse as determined by clinical signs and blood

¹ Moon, V. H., *Ann. Int. Med.*, 1938, **12**, 205; *Shock and Related Capillary Phenomena*, Oxford Univ. Press, 1938.

² Barsoum, G. S., and Gaddum, J. H., *J. Phys.*, 1935, **85**, 1; *Clin. Sci.*, 1936, **2**, 357.

³ Code, C. F., *J. Phys.*, 1937, **89**, 257.

⁴ Barsoum, G. S., and Smirk, F. H., *Clin. Sci.*, 1935, **2**, 353.

⁵ Haworth, E., and MacDonald, A. D., *J. Hyg.*, 1937, **37**, 234.

studies including plasma specific gravity, hemoglobin and hematocrit estimations were studied. In 4 cases, a single determination only was obtained. Control specimens were taken either before operation or after recovery in the remaining 15. These have been divided into 3 groups. Table I gives the histamine values obtained on 8 patients who underwent surgical operation without manifesting any clinical or other signs of shock. One case of severe trauma in a child of 8 is also included.

It will be observed that little or no change in the blood histamine occurred in 5 of these patients. In 2, however, (No. 155 and 162) a moderate decrease occurred. Blood studies were performed simultaneously and in no instance was there any degree of hemoconcentration. One exception in this group is patient No. 96 in whom a single determination only was obtained several hours after operation and the value for blood histamine was 0.015 γ /cc, which is low as compared to the normal average. He did not have any symptoms of shock.

TABLE I.
Blood Histamine in Patients Undergoing Surgical Operation Without Developing Shock.

Case No.	Age	Sex	Operation	Time of specimen	Blood histamine γ /cc
70	30	F	D and C	Control	.05
				1 hr	.03
96	32	M	Nephrectomy	4 hr	.015
117	30	M	Gastric resection	Control	.06
				4 hr	.05
134	34	M	Gastric resection	Control	.065
				1 hr	.075
				2 hr	.05
				24 hr	.05
148	45	M	Gastric resection	Control	.035
				3 hr	.042
155	36	F	Thoracotomy	Control	.062
				3:30 hr	.035
				24 hr	.033
				7 days	.025
				14 days	.042
162	50	F	Cholecystectomy	Control	.06
				2 hr	.05
				24 hr	.04
				2 days	.06
				8 days	.08
93	9	M	Trauma to leg followed by amputation	1 hr after trauma	.04
				1 hr after amputation	.04

TABLE II.
Blood Histamine in Patients Developing Shock Following Surgical Interference.

Case No.	Sex	Age	Operation	Time specimen taken	Signs of shock	Blood histamine γ /cc
20	M	25	Gastric resection	4 hr P.O. 3 days P.O.	+++ Recovered	.01 .05
26	M	21	Bilateral hydronephrosis	6 days P.O.	+++	.02
95	M	42	Gastric resection	12 hr P.O. 6 days P.O.	+++ Recovered	.01 .06
102	M	65	1st stage prostatectomy	5 hr P.O. 48 hr P.O. 7 days P.O.	+++ +++ Recovered	.015 .08 .08
130	M	45	Abdomino-perineal resection	Control 1½ hr P.O. 24 " P.O.	++ ++ Condition good	.035 .01 .04
141	M	48	Acute intestinal obstruction, patient operated on	24 hr P.O. 2 " P.O. 24 " P.O. 48 " P.O. 72 " P.O.	+++ + +++ +++ died	.01 .06 .025 .01
161	F		Gastroduodenostomy	Control 3 hr P.O. 5 " P.O. 24 " " 48 " " 8 days	- ++ ++ - - -	.07 .035 .03 .03 .038 .07
116	M	31	Pyloroplasty	Control 24 hr P.O. 48 " " 7 days 14 " "	- ++ ++ ++ -	.08 .08 .035 .04 .02 .04

TABLE III.
Cases of Traumatic Shock.

Case No.	Sex	Age	Trauma	Time specimen taken	Signs of shock	Blood histamine γ/cc
4	M	28	Industrial accident, hit by falling bricks	4 hrs after	++++	.002
118	M	50	Severe injury to right arm, with hemorrhage Operation amputation of arm	1 hr after trauma 4 hr P.O. 18 " P.O. 20 " "	++++ ++ + died	.11 .04 .02
131	F		Head injury with hemorrhage		+++	.015

Eight patients who exhibited signs of shock following operation are presented in Table II. Six of these showed marked changes in the blood histamine, and this was also accompanied by evidences of hemoconcentration as determined by simultaneous blood studies. It will be observed that as a general rule, the blood histamine is low or decreasing within 2 to 3 hours following the operation and that there is a return to normal or even high levels after varying intervals of time.

In Table III are presented 3 patients admitted following severe trauma. Single determinations only were available on 2 of these, No. 4 and 131, and it will be noted that the blood histamine level is decreased. Case 118 was admitted to the hospital within 45 minutes after having sustained a severe traumatic injury complicated by hemorrhage. A specimen was obtained before any therapy was administered and the blood histamine was found to be 0.11 γ /cc. This is higher than the normal value. Following amputation of the right arm, and administration of cortin intravenously along with a transfusion, the blood histamine was again determined and found to be 0.04 γ /cc. On the following day, a third specimen was found to be 0.02 γ /cc at 10:30 A.M. and at 12:30 P.M. the patient died. It should be noted that in all other cases, the first examination of the blood was done only several hours after the trauma.

A single determination only was obtained in 6 cases in whom death occurred within 3 to 48 hours. These are presented in Table IV and it will be noted that the blood histamine is markedly decreased in all as compared to normal values.

The histamine theory of shock has been rejected by many different

TABLE IV.
Cases in Agonal States.

Case No.	Sex	Age	Diagnosis	Time of death after operation or onset of symptoms	Time before death specimen taken	Histamine γ /cc
86	F	45	Severe burns	7 days	24 hr	.001±
111	F	33	Dehydration colitis		24 "	.015
119	M	40	Mesenteric thrombosis	36 hr	12 "	.015
123	F	35	Extreme cachexia	6 mo	48 "	.001
135	M	60	Ca of stomach		48 "	.01
167	F	30	Pneumonia and peritonitis following appendectomy	7 days P.O.	3 "	.005

workers mainly because of the difficulty of demonstrating the presence of an active depressor substance in the blood of experimental animals or in that of man during shock (Schneider,⁶ O'Shaughnessy and Slome,⁷ Dragstedt and Mead⁸). On the other hand, histamine is looked upon as a factor responsible for the production of symptoms of anaphylactic shock in the guinea pig (Bartosch, Feldberg and Nagel,⁹ Code¹⁰), and in the dog (Dragstedt and Mead,¹¹ Code¹⁰). In both of these species, anaphylactic shock is accompanied by an increase of the blood histamine. Furthermore, there is little difference between the symptoms of anaphylactic shock and histamine shock in either of these species or in the rabbit. Yet, in the rabbit, the onset of anaphylactic shock is accompanied by a marked decrease in the blood histamine (Rose and Weil¹²). This has also been shown to occur in the horse and calf (Code and Hester¹³). It may be of interest to note that according to Moon¹ there is a fundamental similarity in the pathology of anaphylaxis and shock, namely changes in capillary function and endothelium.

Previous reports on the blood histamine in cases of shock due to extensive burns have indicated that there is first an increase of blood histamine followed by a slow return to normal (Barsoum and Gaddum,² Code and MacDonald¹⁴). According to Barsoum and Gaddum there was no relation between this rise and secondary shock. Only one case with severe burns has been available in the present study, in this a simultaneous study of the blood histamine, hemoconcentration and blood electrolytes was made. (Case No. 86). The blood showed marked hemoconcentration, and no histamine was found. This specimen was obtained on the sixth day after the trauma and the patient died 48 hours later.

In view of the above results, there appears to be a mechanism whereby the blood histamine is diminished in conditions where the accepted criteria of shock exist, and in certain other cases shortly before death. The nature of this mechanism is not yet clear, but may possibly be due to a transfer of the histamine of the blood to the

⁶ Schneider, H., *Deutsche Z. f. Chir.*, 1930, **220**, 343.

⁷ O'Shaughnessy, H. L., and Slome, D., *Brit. J. Surg.*, 1935, **22**, 589.

⁸ Dragstedt, C. A., and Mead, F. B., *J. Am. Med. Assn.*, 1937, **103**, 95.

⁹ Bartosch, R., Feldberg, W., and Nagel, E., *Arch. f. d. ges. Physiol.*, 1932, **230**, 129.

¹⁰ Code, C. F., *Am. J. Physiol.*, 1939, **127**, 78.

¹¹ Dragstedt, C. A., and Mead, F. B., *J. Pharm. and Exp. Ther.*, 1936, **57**, 419.

¹² Rose, B., and Weil, P., *Proc. Soc. Exp. Biol. and Med.*, 1939, **42**, 494.

¹³ Code, C. F., and Hester, H. R., *Am. J. Physiol.*, 1939, **127**, 71.

¹⁴ Code, C. F., and MacDonald, A. D., *Lancet*, 1937, **233**, 730.

damaged area or to certain of the abdominal viscera. This may possibly account for the failure to demonstrate an increase in the histamine content of the blood when shock is well established, although some of the cases indicate that there may be an early increase. It may be that there is first a liberation of histamine which is rapidly followed by a decrease of the blood histamine below the normal value. This could be accounted for if one assumed that the histamine gathers in the tissues, or traumatized area, as it does in areas of inflammation (Tarras-Wahlberg,¹⁵ Rocha e Silva and Bier¹⁶). Furthermore, in dogs it has been shown that following burns there is first an increase of the blood histamine, followed by a disappearance in a matter of 2-3 days, accompanied by an increase in the histamine content of the spleen, liver and pancreas (Kisima¹⁷). There is a marked similarity between adrenal insufficiency and shock and it has been demonstrated that the histamine content of the gastro-intestinal tract increases to 250% over the normal in adrenalectomized rats, although there is little change in the blood histamine of these animals.

It should be pointed out that although the blood histamine is markedly diminished in patients where shock is established, such a diminution may occur in certain other conditions in cases of allergy. In these latter states, however, one does not observe as marked a variation in the histamine content of the blood. This will be discussed in a subsequent communication.

Conclusions. In a series of patients in varying types of shock manifested by clinical signs, hemoconcentration, and lowering of the B.P. the total blood histamine has been determined. The results indicate that in the cases studied a marked diminution of the histamine content of the blood occurs when shock is established as compared with control values and those after recovery. There appears to be some correlation between the severity of the shock and the degree of blood histamine decrease. Blood histamine has also been found to be low in agonal states. The significance of these findings is discussed.

¹⁵ Tarras-Wahlberg, B., *Klin. Wschr.*, 1937, **16**, 958.

¹⁶ Rocha e Silva, M., and Bier, O., *Arq. do Inst. Biology*, 1938, **9**, 123.

¹⁷ Kisima, H., *Fukuoka Acta. Medica*, 1938, **31**, 49.