THE TOXIN OF BURNS

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The theories explaining the toxic manifestations following extensive burns are (Harkins[4]):

(1) *Physical,* in which there is a local leakage of plasma into the tissues altering the circulation and resulting in a diminished blood volume, a diminished cardiac output, and finally a collapse of the blood pressure (the diminished blood volume is accompanied by an increased concentration of blood and hemoglobin).

(2) *Toxic,* whereby the supposed toxemia caused by the burn results, after a certain time, in shock and death.

Whereas the earlier authors (Parascandolo,[12] Pfeiffer,[14] Lewis and Grant[9]) demonstrated the presence of a toxic substance in the blood of burned individuals (later Robertson and Boyd,[15] Shimada,[17] Nagamitu[10]), the more recent authors question the presence of a toxin (Harrison and Blalock,[7] Harkins,[5] Wilson and Stewart, Underhill and Kapsinow[18]). Indeed, Underhill and Kapsinow emphasized that as long as we entertain the idea of a burn toxin, the progress in the understanding of burns and its therapy will be delayed.

One of the important factors in the modern concept of the pathogenesis in burns (and traumatic shock) is that there is a local accumulation of fluid which begins immediately or shortly after the injury, and continues thereafter, resulting in a decrease of the blood volume and an increase in the blood concentration. According to Harkins and others, if the process is too severe, the cardiac output decreases, and when this reaches one-third its normal, the blood pressure falls and death ensues as a result of cardiac failure—secondary shock (Underhill, Kapsinow and Fisk, Blalock, Harkins for burns; and Roome, Keith and Phemister,[16] Parsons and Phemister[13] for traumatic shock).

The protagonists of the toxic theory have offered many possibilities as to the nature of this toxin. Parascandolo links it to the ptomaines. Pfeiffer believes it resembles the nucleoproteins of snake venom. Robertson and Boyd believe it to be primary and secondary proteoses. The latest concept is that it is histamine-like in character because it effects a drop in blood pressure (rabbits and cats), and it contracts smooth muscle (uterus, intestinal strip—Shimada, Nagamitu).

The following experiments were undertaken to determine whether or not

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histamine-like substances were present in the blood of burned animals or humans.

METHOD.—Blood was drawn from burned (anesthetized) shoats (size of burn = 100 to 250 square inches), adult pigs (size of burn = 100 to 550 square inches), and guinea-pigs (size of burn = 4.8 to 9.6 square inches) at regular intervals in the course of the experiment. The tail method for obtaining blood was used for the shoats and adult pigs. Blood from humans (adults and children) was obtained at varying intervals after burns (three days to 13 months). In one case of traumatic shock, blood was obtained two hours after injury.

Serum, red blood cells, citrated blood, and hemolized blood were examined for their ability to contract a virgin guinea-pigs' (200 to 300 Gm.) uterus (method of Dale and Laidlaw[1]). The uterus-ovary preparations were suspended by means of glass hooks to a suitable lever and immersed in 35 cc. of Ringer-Locke's solution (aerated). The lever was approximated to a kimograph, and the oscillations of the lever recorded. The removal of fluid or addition of same into the preparation was accomplished by suction and delivery applied to the bottom of the tube. In this way the muscle preparation was never molested and suffered minimal extraneous irritations. The Ringer-Locke containing tube was immersed in a constant water bath (37° C.), and all solutions added to the fluid were first warmed to the same temperature. After suspending the uterus-ovary preparation, about 15 to 20 minutes were allowed for relaxation of the muscle. The latter being attained, the next step in all instances was to add 1 cc. of a 1:100,000 histamine solution, made up in Ringer-Locke's. (This amount gave the most satisfactory contraction to the uterus as indicated by the lever rise.) The height of the elevation produced by histamine was used as a basis of comparison. After each procedure the specimen was washed three times, using from 100 to 150 cc. of Ringer-Locke solution. Relaxation to the original base line was effected before another testing solution was added (15 to 30 minutes). At the end of each experiment, the action of histamine was again determined.

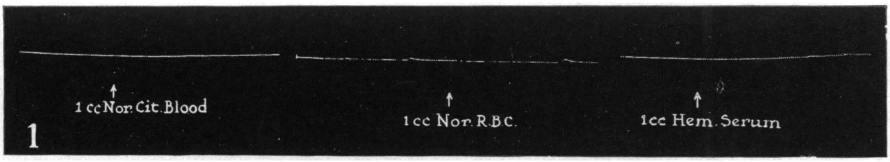
Sterile blood specimens were collected and kept in the ice-box until used. Every specimen (except those used immediately after bleeding) was treated with phenol (0.5 per cent), or a few drops of chloroform added (three drops to 20 cc.) to prevent bacterial activity.

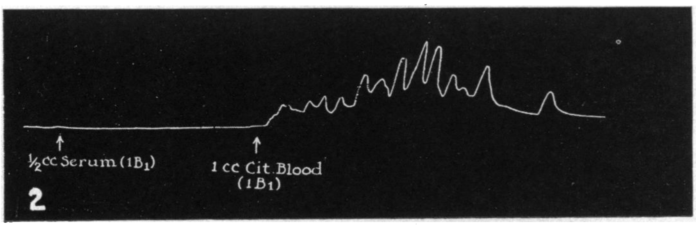
RESULTS.—*(I) Normals:* The serum, citrated blood, washed red blood corpuscles, or hemolyzed serum obtained from normal shoats, adult pigs (Fig. 1), guinea-pigs and humans did not contract the virgin guinea-pigs' uterus as noted by the kimograph tracings. Examinations were made from one to 24 hours after withdrawal of blood.

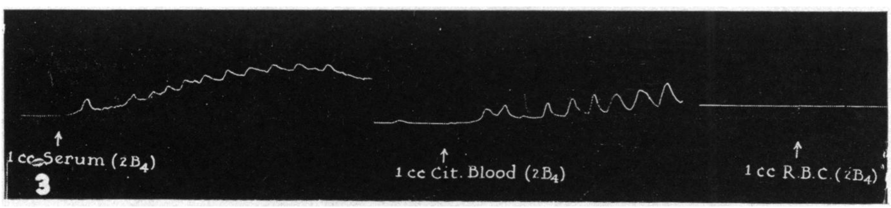
(II) Burned Cases.—Shoats: As a rule, smooth muscle contracting substances were detected in the blood of burned shoats one hour after the beginning of the experiment (Fig. 2). At this time only the citrated blood and the R.B.C. contained the active principle. From 18 to 24 hours later this substance was found mainly in the serum (Fig. 3). Traces of an histaminoid

substance were at times noted in the R.B.C. up to two weeks, but this was not the rule. From 20 to 28 days this substance could not be detected by the above method (Table I). (The wounds by this time had healed under a scab without infection.)

Adult Pigs.—After apparent healing of the burned sites (one month after the onset of the experiment), large slices of scarred areas, including skin and subcutaneous fat, were removed for microscopic section. Because of the







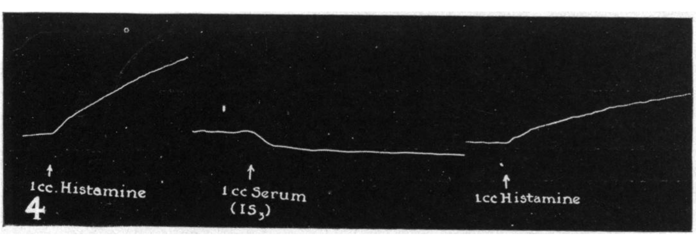


FIG. 1.—The action of normal blood on the virgin guinea-pig uterus.
FIG. 2.—The action of burned shoat blood (1 hr.) on the virgin guinea-pig uterus.
FIG. 3.—The action of burned shoat blood (19 hrs.) on the virgin guinea-pig uterus.
FIG. 4.—The action of burned shoat blood (3 da.) on the virgin guinea-pig uterus.

numerous burn sites, approximately 15 to 25 square inches were removed from each pig. These wounds were slow in healing. Two of three pigs thus treated contained in their serum smooth muscle contracting substances five months after the last burn and two months after the removal of the biopsies. The wounds had superficially healed in all cases when blood was first withdrawn, but it was difficult to decide whether or not the processes of healing and absorption were still going on beneath the superficial approximation.

TABLE I

THE PRESENCE OF AN HISTAMINOID SUBSTANCE IN THE BLOOD OF BURNED SHOATS

Time after Burn	Action on Virgin G. P. Uterus S.	cit. b.	R.B.C.	Time after Burn	Action on Virgin G. P. Uterus S.	cit. b.	R.B.C.
0.......	0	0	0	0.......	0	0	0
1 hr.....	0	++	—	2 hrs....	0	++	+
18 hrs.....	0	++	—	19 hrs....	+++	tr.	0
27 hrs.....	+++	+	—	45 hrs....	0	0	0
44 hrs.....	+++	+	—	3½ da...	++	++	0
5 da.....	+++	tr.	++	8 da.....	++	+	0
2 wks....	++	+	—	20 da.....	0	0	0
28 da.....	0	0	0.				
40 da.....	0	—	—				

++ = action of 1 cc. of a 1:100,000 histamine solution; S = serum; cit. b. = citrated blood; R.B.C. = red blood corpuscles; tr. = trace; the negative sign (—) indicates test not performed.

TABLE II

THE PRESENCE OF AN HISTAMINOID SUBSTANCE IN THE BLOOD OF BURNED GUINEA-PIGS

No.	Size of Burn (sq. in.)	1 hour	5 days	25 days
13	8.40	0 (cit. b.) tr. (R.B.C.)	+ (S.) +++ (R.B.C.)	
371	7.04	+ (cit. b.)	++ (R.B.C.) tr. (S.)	
321	8.40	0 (cit. b.)	tr. (S.)	0 (S.)
19	8.32	0 (cit. b.) tr. (R.B.C.)	+ (R.B.C.)	0 (S.)
265	8.96	0 (cit. b.) tr. (R.B.C.)		
23	7.84		0 (S.) ++ (R.B.C.)	
330	7.68	++ (cit. b.)	++ (R.B.C.)	
235	8.16	tr. (S.) ++ (R.B.C.)		
82	8.96	+ (R.B.C.)		
227	4.80	+ (cit. b.)		
25	7.36	++ (cit. b.)		
234	4.80		+ (R.B.C.)	0 (S.)
338	8.32		++ (R.B.C.)	
333	9.60	0 (cit. b.) tr. (R.B.C.)	0 (S.)	0 (S.)

++ = action of 1 cc. of a 1:100,000 histamine solutions; S. = serum; cit. b. = citrated blood; R.B.C. = red blood corpuscles; tr. = trace.

Guinea-Pigs.—One hour after the beginning of the experiment, an histaminoid substance was demonstrable in the R.B.C. After five days the serum, too, contained this element, but not to the extent of that found in the R.B.C. After 25 days the specimens examined (serums) were devoid of active principles.

Humans.—Table III summarizes the effect of the blood on the guinea-pigs' uterus. An histaminoid substance was not detected until five days following a burn. With healing, these bodies were found only in traces by the third to fourth week, whereas if the wound was more extensive and healing slow (usually associated with a slight infection) this substance persisted for a longer period of time.

Table III

THE PRESENCE OF AN HISTAMINOID SUBSTANCE IN THE BLOOD OF BURNED HUMANS

Name	Age—Sex	Time after Burn	Action on Guinea-Pigs' Uterus	Size and Condition of Burn
F. Z.	46—M.	—	0 (S.)	Normal
R. T.	31—M.	3 da.	0 (S.)	Chest and left arm—2nd degree
H. J.	65—M.	5 da.	tr. (S.)	Both hands—2nd degree
N. K.	39—F.	19 da.	+ (S.)	Both legs—2nd and 3rd degrees
C. I.	35—M.	22 da.	tr. (S.)	Arm and back—2nd degree. Slight infection; healing rapid
S. P.	36—M.	25 da.	tr. (S.)	Legs and arms—2nd degree. Slight infection; healing rapid
D. D.	21—M.	27 da.	++ (S.)	Legs—2nd degree. Slight infection; low grade temperature
P. G.	65—M.	34 da.	+++ (S.)	Arms and legs—2nd degree. Wounds clean; healing
R. C.	8—F.	37 da.	+ (S.)	Neck, abdomen and thigh—2nd degree. Slight infection, slight temperature
M. M.	9—F.	68 da.	+ (S.)	Right chest and arm—2nd degree. Slight infection, but healing
C. P.	40—M.	13 mos.	tr. (S.)	Keloids of abdomen and thigh. Recently healed graft
E. S.	15—M.	2 hrs.	+ (S.)	Shock due to multiple fractures

++ = action of 1 cc. of a 1:100,000 histamine solution; S. = serum; R.B.C. = red blood corpuscles; tr. = trace; F. = female; M. = male.

Discussion.—As the experimental data indicate, there appears in the blood of burned animals (shoats, pigs and guinea-pigs) and humans a substance which causes contraction of the guinea-pigs' uterus.

This substance was first linked with the R.B.C., and after 18 to 24 hours was found in the serum (shoats). In guinea-pigs the R.B.C. were found to contain an histaminoid substance up to five days. In humans an histaminoid substance was not present until five days after the burn. In one case of shock, examined early, this substance was detected. Normal serums of animals or humans examined fresh or after one to 14 days did not contain histaminoid substances.

The intraperitoneal injection of 2 cc. of burned swine serum into guinea-pigs was without noticeable effect. However, burned guinea-pigs injected with this same serum subcutaneously undermining the wound or intraperitoneally (unheated or heated at 60° C. for half an hour) resulted in the death of four out of six guinea-pigs. On the other hand, burned guinea-pigs treated similarly with saline (eight pigs) and normal serum (four pigs) remained immune. Postmortem examination of the guinea-pigs revealed a marked dehydration and hyperemia of the internal organs with a slight ecchymosis. The lungs were not distended.

The ability of this burn toxin to contract the virgin guinea-pigs' uterus would naturally associate it with histamine, for the latter substance has the same properties. Yet points of divergence were noted. When the blood of pigs containing this histaminoid substance was heated for half an hour at 60° C., it lost its ability to contract the guinea-pigs' uterus. Histamine so treated retained this potency (150° to 170° C. decreases the action of histamine according to Feldberg and Schilf[3]). Furthermore, upon several occasions after adding the burn toxin to the muscle preparation, a contraction as usual resulted, but after washing and again adding the same serum a demonstrable contraction failed to appear. Histamine in such instances caused a definite contraction if added immediately after the above or after washing (Fig. 4).

Comment.—Histamine-like substances are supposedly present in the normal blood but in an inactive form (Feldberg and Schilf). Histamine, if injected slowly, in many times its lethal dose, cannot be detected in the blood of rabbits (Oehme,[11] von Guggenheim and Loeffler[19]). Supposedly the lung and the liver remove this substance very rapidly from the blood stream. Some animals are more susceptible to histamine than others, the mechanism not being understood. The differences in animal susceptibility may account for the variations in the amount of histaminoid substance in the blood of the pig and in the human following burns. Why the 45 hours blood specimen of the shoat studied did not contract the guinea-pigs' uterus and the three and one-half day specimen did, cannot be explained.

Lewis and Grant[9] described an histamine-like substance ("H" substance) as a normal product of the skin, and upon irritation of the latter large quantities of the former may be liberated. Harris[6] has isolated as much as 10 mg. of histamine per kilogram of human skin. Most authors are agreed that histamine causes an increased permeability of the capillaries resulting in an exudation of plasma and retardation of the blood flow through the capillaries (Dale and Laidlaw, Feldberg and Schilf). In sufficient quantities histamine causes a decrease in blood volume and an increase in hemoglobin concentration as a result of the above mechanism (Dale and Laidlaw, Eppinger and Schürmeyer,[2] Lamson, Abt, Oosthuisen and Rosenthal[8]). This action, as has already been stated, is precisely what occurs following burns, according to the protagonists of the physical theory.

SUMMARY.—In the blood of burned shoats, adult pigs, guinea-pigs and humans, a substance was found that caused contraction of the virgin guinea-pigs' uterus. This substance was at first linked with the red blood corpuscles, but was later found in the serum. The above differs from histamine in that it is heat labile and it does not act upon the virgin guinea-pigs' uterus under certain conditions when histamine does.

It was noted that the local action of histamine is similar in many respects to the local pathology in burns and shock.

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