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Relation of Anemia and Hemorrhagic Shock to Experimental Ulcer Production.*

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The occurrence of acute ulcers in the upper gastrointestinal tract of humans has been reported by several authors[1-3] as sequelae of many diverse clinical conditions such as extensive surgical procedures, burns, fractures, diabetic acidosis, freezing, severe heart disease, and other grave systemic disorders. They noted that all of these cases had as a common denominator the factor of shock. It is our purpose to indicate some observations on the effect of anemia and post-hemorrhagic shock on the histamine-provoked ulcer in dogs.

Method. Fifty-one healthy dewormed dogs of medium size from 1 to 5 years of age were used in these experiments. The stimulus for ulcer production was provided by a daily intramuscular injection of 30 mg of histamine-base in beeswax after the method described by Code and Varco.[4] Feed pans were removed in the evening at the time of injection and the animals were not fed again until morning. Those animals not succumbing to ulcer formation were sacrificed 12 hours after the last histamine injection by intravenous sodium pentobarbital.

Experiment I. Fifteen dogs were bled acutely from the femoral artery or vein until an average of 42% of their estimated blood volume was removed. The withdrawal of this volume of blood uniformly leads to blood pressures of shock level. Histamine-in-wax injection was then started the first or second day following the bleeding. Six of these animals as indicated in Table I were bled under pentobarbital anesthesia with continuous kymographic recording of their blood pressure from the carotid artery. In these 6 dogs the blood pressure was maintained below 50 mm of mercury for periods from 30 to 55 minutes and then allowed to rise or was elevated by normal saline intravenously. The remaining 9 dogs were bled to shock level without anesthesia and without blood pressure recordings. Then quantities of saline solution varying from none to an amount equal to the volume of the blood withdrawn were injected intravenously as indicated in Table I. The period of shock in these dogs was relatively shorter than the above-mentioned 6 bled under anesthesia inasmuch as the saline intravenously was started immediately following the finish of rapid continuous blood withdrawal from the femoral vessels. All dogs in Experiment I had blood samples drawn for hemoglobin, hematocrit, and total protein levels before bleeding and at daily intervals thereafter. In those dogs in which the blood volume was not actually measured by the dye method, we used 10%[5] of their body weight as our criterion for estimating the total circulating blood volume. These above-mentioned differences in procedures are indicated in Table I.

Experiment II. In 13 dogs a chronic anemia without shock was produced by removing small quantities of blood (100-150 cc) not oftener than every 24 hours over a period of from 5 to 30 days. Observations were made also on hemoglobin, hematocrit,

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TABLE I.
Production of Ulcer in Dogs Following Acute Hemorrhage with Shock.
(30 mg histamine-base in beeswax daily).

Dog No.	% bl. vol. withdrawn	Duration of shock min.	cc-saline replaced	12 hr after bleeding: g Hbg.	12 hr after bleeding: cc/100 Hct.	No. hist. inject.	Results
954*	30	42	—	13.1	41	5	Perf. duod. ulcer. Gastric erosions
968*	34	55	250	10.4	32	4	Negative G. I. T.
377	36	30	100	8.0	31	5	" " " "
386	53	30	150	10.3	35	5	Two duod. ulcers
438	34	30	400	7.2	31	5	Petechial hemorrhages in antrum
439	28	30	450	9.7	33	5	Six small duod. erosions
889	57	—	—	—	—	1	Prepyloric ulcers. Multiple antral petechia
892	52	—	—	8.4	29	5	Negative G. I. T.
899	29	—	—	15.1	48	5	Perforated duod. ulcer
906	53	—	500	9.6	32	4	" " "
917	72	—	850	6.6	22	8	Multiple antral erosions
935	48	—	250	10.0	34	4	Antral ulcer and erosions
946	14	—	—	9	35	5	Two large duod. ulcers
947	51	—	225	8.4	28	5	Negative G. I. T.
959*	44	—	—	8.5	34	6	Perforated gastric ulcer

* Blood volume measured before and after bleeding.

No. of dogs injected	15
" " " with ulcer	8
" " " with erosions	3
" " " with perf. ulcers	4

TABLE II.
Production of Ulcer in Dogs with Chronic Anemia (No Shock).
(30 mg histamine-base in beeswax daily).

Dog No.	Init. wt, lb	Total amt. bl. withdrawn, cc	Bleeding period, days	At onset hist. inj.: Hbg., g	At onset hist. inj.: Hct., cc/100 cc	No. inj. hist.	Results
900	36	1050	7	11	32	8	Neg. G. I. T.
977	41	1135	9	9.6	31	5	" " " "
988	25	780	6	6.6	23	5	" " " "
10	30	1500	9	5.2	21	5	" " " "
9	35	1250	14	7.2	27	5	Single duod. ulcer
45	28	2500	30	6.1	31	5	Duod. and jejunal ulcers
53	39	1600	9	7.2	27	5	Duod. ulcers
99	30	1150	8	6.1	24	5	Shallow duod. ulcer
138	28	1300	10	6.5	25	5	Neg. G. I. T.
372	30	800	8	6.8	29	3	Neg. G. I. T. Sev. pneumonia
373	28	1035	8	6.6	24	5	Neg. G. I. T.
397	28	950	5	6.6	24	5	" " " "
404	28	800	5	5.8	24	5	" " " "

No. of dogs injected	13
" " " negative	9
" " " with ulcers	4

and total protein levels before bleeding and daily thereafter. Blood pressures before and after bleeding were recorded by means of an exteriorized carotid artery loop in one dog and by femoral artery punctures in another.

Experiment III. Seven dogs were bled to shock level under sodium pentobarbital anesthesia with continuous blood pressure tracings. In 5 of these animals the blood pressure was maintained below 50 mm mercury for at least 30 to 40 minutes, and in the other 2 dogs the period of shock was shortened to 10 to 12 minutes. Then all dogs were given their own citrated blood back intravenously. Two and

TABLE III.
Production of Ulcer in Dogs Subjected to Shock (No Anemia).
(30 mg histamine-base in beeswax).

Dog No.	Wt	Duration of shock, min.	No. hist. injections	After shock: g Hbg.	After shock: Het. cc/100 cc	Results
971	47	less than 10	5	12.8	43	Negative G. I. T.
995	40	40	6	14.9	49	Duodenal ulcer
1	39	12	6	16.6	58	Negative G. I. T.
378	20	30	5	11.0	37	Perforated duod. ulcer
383	29	30	5	11.0	45	Negative G. I. T.
436	18	30	3	16.0	51	Penetrating antral ulcer, duod. ulcers
437	28	30	5	14.4	46	Negative G. I. T.

No. of dogs tested 7
" " " with ulcer 3
" " " with perforated ulcer 1

TABLE IV.
Production of Ulcer in Normal Dogs.
(30 mg histamine-base in beeswax daily.)
Control Series.

No. of dogs	No. hist. injections	No. dogs with: Ulcer	No. dogs with: Erosion
16	5	2	1

one-half g of citrate was the maximum amount given to any dog.

As additional controls for this experiment, 2 animals were anesthetized and given an equal quantity of sodium citrate intravenously and a third dog was anesthetized and a laparotomy was performed. These 3 animals were then started on histamine-in-wax injections the following day and when sacrificed after 5 consecutive histamine injections all 3 had normal gastrointestinal tracts. In addition, 13 dogs of comparable size and age were given 5 to 6 consecutive daily injections of histamine-in-wax and sacrificed as controls. The data for this control group are listed in Table IV.

Results. The incidence of ulcerations in Experiments I, II, and III is shown in Tables I, II, and III, respectively. It is apparent that the dogs subjected to both anemia and shock were the most susceptible to ulcer formation. Inspection of Tables I and III would seem to indicate that the duration of shock within the limits tested in these experiments does not make a great deal of difference in ulcer incidence, a relatively short insult being as effective in abetting the ulcer diathesis as one lasting 30 to 40 minutes. Nor does the factor of saline replacement seem to affect the ulcer diathesis. The hemoglobin and hematocrit values shown in Table I are those taken approximately 12 hours after bleeding and subsequent determinations for most all of the dogs showed a progressive fall in the hemoglobin values and hematocrit levels for the first 3 to 4 days after bleeding. Moreover, inspection of these values suggests that the dogs having the greatest reduction in hemoglobin levels and hematocrit values had the least severe ulcers. This fact naturally suggested an attempt to separate the effects of the factors of anemia and of shock. In Experiment II we did not observe any blood pressure values to fall below 90 mm Hg so that we have anemia production uncomplicated by shock. Here the incidence of ulcers was somewhat higher than that observed in the control group of dogs (Table IV). However, in Experiment III, where hemorrhagic shock was produced by bleeding and then the resultant anemia corrected by giving the animals their own blood back, the incidence of ulcer approached that seen in Experiment I, indicating that of the 2 factors shock has the,

greater effect in abetting the ulcer susceptibility.

Discussion. The ulcer abetting effect of shock is amply corroborated by both experimental and clinical evidence. Moon[6] lists gastric erosions and ulcers as a pathological feature of shock of any kind. Price[7] *et al.* in their studies on post-hemorrhagic shock observed subserous and submucous hemorrhages with bleeding into the lumen of the gastrointestinal tract in occasional dogs dying without therapy. Blalock[8] has observed the same gastrointestinal tract findings in his dogs following post-hemorrhagic shock.

The above-mentioned investigators and others agree that the characteristic physiologic responses to a large blood loss in surviving animals are anemia, hemodilution, and vasoconstriction. Our observations indicate that the factors of anemia and hemodilution are common to the dogs in both Exp. I and II, yet there is a pronounced difference in the ulcer incidence indicating to us that the ulcer abetting effect of post-hemorrhagic shock is a vascular one, namely, vasoconstriction. Klemperer[9] *et al.* in studying the gastrointestinal manifestations of shock in humans has claimed to be able to reproduce in animals all of the pathology seen in their autopsy material by causing visceral vasospasm by repeated intraperitoneal injection of epinephrine. Likewise the potent ulcer abetting effects of adrenalin-in-beeswax and pitressin-in-beeswax have been studied in this laboratory by Baronofsky and Wangensteen.[10] It was their conclusion that the chronic arterial spasm invoked by epinephrine or pitressin produces local areas of anemic gastric mucosa which then became susceptible to the acid-peptic activity of the gastric juice. A somewhat analogous condition also studied in this laboratory is the production of ulcers and erosions by plugging the end vessels of the upper gastrointestinal tract with the intravenous injection of fat.[10] Knisely[11] *et al.* have demonstrated in healthy unanesthetized human blood donors the intense vasoconstriction that occurs in the arteries, arterioles and capillaries of the bulbar conjunctiva following a moderate blood loss. Reasoning from the demonstrated role of hemoconcentration[12] in aiding and abetting the ulcer diathesis, it might be expected that hemodilution would have a potent analogous effect, but such does not appear to be true in our experience, for the dogs in Exp. II show a fairly uniform degree of hemodilution without a striking increase in their ulcer incidence.

Conclusions. The factors of post-hemorrhagic anemia and shock are evaluated in relation to their effect on the histamine-provoked ulcer in dogs. Our evidence indicates that anemia and hemodilution occurring without shock is a mild ulcer abetting factor. However, post-hemorrhagic shock, even of relatively brief duration aids and abets the ulcer susceptibility most likely through its vasoconstrictor effect on the small blood vessels with resultant localized anemic areas in the mucosa.

The combined effects of post-hemorrhagic anemia and shock on the ulcer diathesis are synergistic in that together they give a higher incidence of histamine-provoked ulcer than does either alone.

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