bicarbonate treated material was placed in 5 cc of thrombin solution the resulting pH was 8; but the thrombin activity disappeared even though the acidity had been controlled properly. The nature of the destructive factor(s) is not known.

Summary. Oxidized cellulose injures thrombin due to its acidity. After neutralization with sodium bicarbonate it can be mixed with thrombin without altering activity. Highly oxidized cellulose contains products capable of destroying thrombin even in neutral solutions.

14599

Influence of Anesthesia on Circulatory Changes in Dogs Subjected to Graded Hemorrhage.*

B. W. ZWEIFACH, S. G. HERSHEY, E. A. ROVENSTINE AND R. CHAMBERS.
From the Department of Biology, Washington Square College, New York University, and the Department of Anesthesia, New York University College of Medicine, New York City.

One of the chief difficulties in a study of the shock syndrome in dogs has been the lack of a critical evaluation of the effects introduced by the anesthetic agent. This paper deals with an analysis of the effects of several anesthetic procedures on the circulatory changes in the dog resulting from a standardized bleeding procedure. By using the changes in the omental circulation as an index it was found that criteria, previously established,[1,2] served as a means of differentiating between specific effects of different anesthetic agents.

Method. Fifty-three dogs were anesthetized with the 6 different drugs indicated in Table I: (1) procaine—local anesthesia, (2) morphine sulphate, (3) cyclopropane, (4) ether, (5) sodium pentobarbital, (6) sodium pentothal. Before anesthesia was induced the femoral artery was cannulated during local procaine infiltration (2 cc of 1% solution). Blood pressure were recorded continuously. Following induction of anesthesia the omentum was exteriorized for direct microscopic study according to a method previously described.[3] In Group 1, (Table I), which served as controls, pain relief for the required surgery was obtained with an abdominal field block using 8-10 cc of a 1% procaine solution. Group 2 was sedated with morphine sulphate given intravenously (2 mg/kg). Groups 3 and 4 were anesthetized with cyclopropane and ether respectively, administered with oxygen. The endotracheal to and fro absorption technic was employed. They were maintained unconscious, in upper first plane surgical anesthesia throughout.[4] Group 5 received a single intravenous dose of 25-30 mg/kg of sodium pentobarbital. Oxygen by endotracheal catheter was given to 3 dogs in this group. As no demonstrable differences were noted in the dogs with or without oxygen in this group, the results are considered together. Group 6 received sodium pentothal (1% solution) intermittently by vein to maintain a similar degree of narcosis and required an average of 10.8 mg/kg/hr. All of this group were given oxygen. Hemorrhage in each instance was accomplished with an initial blood-loss of 2% body weight and continued by removing an additional 0.5% at successive 30-minute intervals. To standardize the procedure, the maximal blood-loss compatible with viability was considered to be that which brought about a cessation of blood-flow in the larger omental arteries under observation during the bleeding. The majority of the dogs lived for at least 60

* The work described in this paper was supported in part by the Josiah Macy, Jr., Foundation.

1 Zweifach, B. W., Lee, R. E., Hyman, C., and Chambers, R., *Ann. Surg.*, in press.

2 Zweifach, B. W., Lowenstein, B. E., and Chambers, R., *A. J. P.*, in press.

3 Chambers, R., and Zweifach, B. W., *Am. J. Anat.*, in press.

4 Guedel, A. E., *Inhalation Anesthesia*, Macmillan and Company, 1937.

TABLE I.
Data on Dogs Subjected to Hemorrhage During Various Anesthetic Procedures.

Anesthesia	No. of dogs	Normal mean B.P.	Hematocrit (%)	Plasma protein (g %)	Anesthetic dose	Oxygen	Blood-loss (% body wt)
Procaine (Abdominal Block)	13	147 mm	50 ± 3	6.0 ± 0.5	8-10 cc	none	5.30
Morphine Sulphate	10	142 mm	45 ± 3	5.8 ± 0.5	2 mg/kg	none	4.60
Cyclopropane	9	152 mm	43 ± 6	5.55 ± 0.5	Upper 1st plane Surgical Anes.	used	4.78
Ether	5	139 mm	49 ± 2	5.67 ± 0.3	Upper 1st plane Surgical Anes.	used	4.10
Pentobarbital	10	147 mm	44 ± 1	5.80 ± 0.4	25-30 mg/kg	used in 3	3.70
Pentothal	6	164 mm	48 ± 3	5.76 ± 0.4	10.8 mg/kg/hr	used	3.80

TABLE II.
% Drop in B.P. from Initial Level at Various Degrees of Blood-Loss.

% Blood-Loss	0	2	2.5	3	3.5	4	4.5	5	5.5	Critical B.P. level mm	Status following last bleeding
Abdominal Field Block	0	17	—	35	37	51	59	62	62	35-45	Maintained for > 2 hr.
Morphine	0	16	—	25	32	39	46	51	45	40-50	Fell to extreme hypotensive levels in 90 min.
Cyclopropane	0	25	58	37	44	48	56	63	69	35-45	Maintained, tended to rise
Ether	0	16	28	36	52	42	50			75-85	Fell to extreme hypotensive levels in 42 min.
Pentobarbital	0	19	31	37	51	52	64			55-65	Fell to extreme hypotensive levels in 45 min.
Pentothal	0	29	49	44	45	45	40			80-90	Fell abruptly to extreme hypotensive levels in 63 min.

to 90 minutes after the final bleeding, those surviving for two hours, at which time observations were discontinued, being sacrificed. No sustaining infusions were used.

Results. Changes in the omental circulation were correlated with blood pressure changes at specific degrees of blood loss. The omental criteria studied were (a) the degree of curtailment of capillary blood flow, (b) the deviations in the minimal reactivity of the muscular components of the bed to the topical application of epinephrine, and (c) changes in the vasomotion of the central muscular channels. The term "vasomotion" is applied to the cyclic contraction-relaxation pattern which characterizes these vessels.[3]

Toleration of Blood-Loss. The ability of the dog to withstand hemorrhage varied significantly with the anesthetic agent used (Table I). Maximal blood-loss (5.3% of body weight) was obtained in the local anesthesia group. The dose of morphine used, although it produced only a euphoric state, significantly lowered the ability of the dogs to tolerate blood-loss. Of the 4 groups subjected to inhalation or intravenous anesthesia, those given cyclopropane were more nearly able to tolerate the maximal blood-loss, while those receiving barbiturates withstood the least hemorrhage.

Inadequacy of Blood Pressure as Criterion. The fall in blood pressure following equivalent bleedings varied considerably. No accurate correlation could be made between the blood pressure levels corresponding to equivalent blood-loss during anesthesia with any one agent or with different anesthetic procedures (Table II). The blood pressure served as a poor index of the dog's ability to withstand additional hemorrhage and was an unreliable prognostic indication of survival time.

In general (Table II), for each anesthetic group, different critical blood pressure levels were noted below which the animal's condition deteriorated rapidly. With pentothal and ether this critical level was reached with relatively high blood pressures (65-75 mm). With cyclopropane and local anesthesia it was not obtained until lower levels (35-45 mm) were reached.

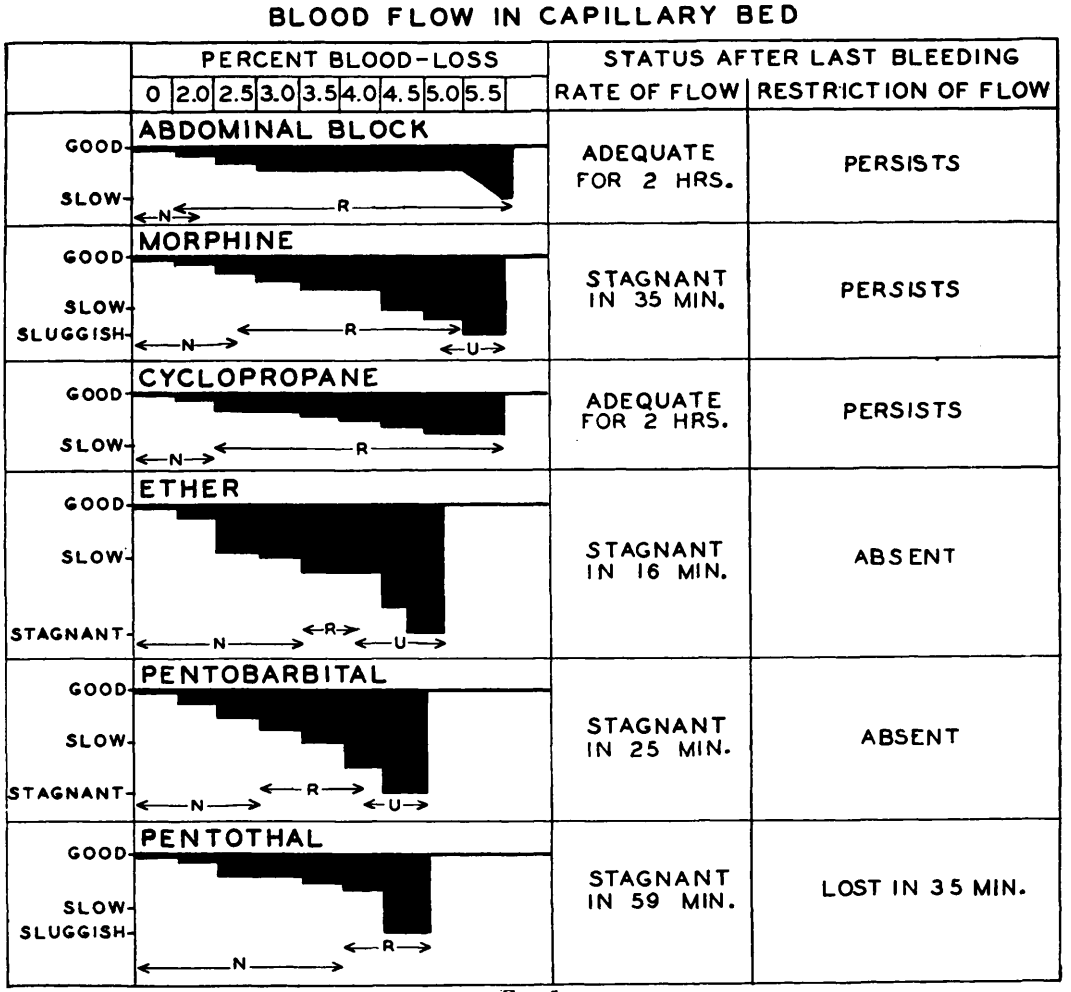

FIG. 1.

Changes in rate and distribution of capillary flow with respect to successive bleedings are shown; the degree of slowing by the deviation below the normal base line; the number of vessels open to the circulation by the symbols "N," "R," and "U." N = the normal condition, with an intermittent flow only through most capillaries. R= the restricted condition, with flow through most direct channels. U = unrestricted condition, with widespread flow through all capillaries.

Capillary Blood Flow. As noted in Fig. 1, the blood flow in the omentum varied considerably with the different anesthetic procedures. The feature which reflected most closely the ability of the dogs to withstand progressive hemorrhage was the persistence of a good flow in the capillary bed. This depended not only upon the rate of flow but on the number of capillaries containing an active circulation. As the hemorrhage approached maximal volume, the omental circulation slowed significantly in all groups (Fig. 1). In those groups which showed high blood-loss figures (control, cyclopropane, morphine), the omental blood flow remained adequate for the longest time. In those groups which showed low blood-loss figures, the last bleeding was followed by the development of a poor capillary circulation, with stagnation in many of the venules and backflow from the larger veins. Such a condition invariably indicated incipient circulatory failure. This occurred in the ether and pentothal groups despite the maintenance of relatively high blood pressures (75-90 mm).

In addition to a slowing of the blood flow,

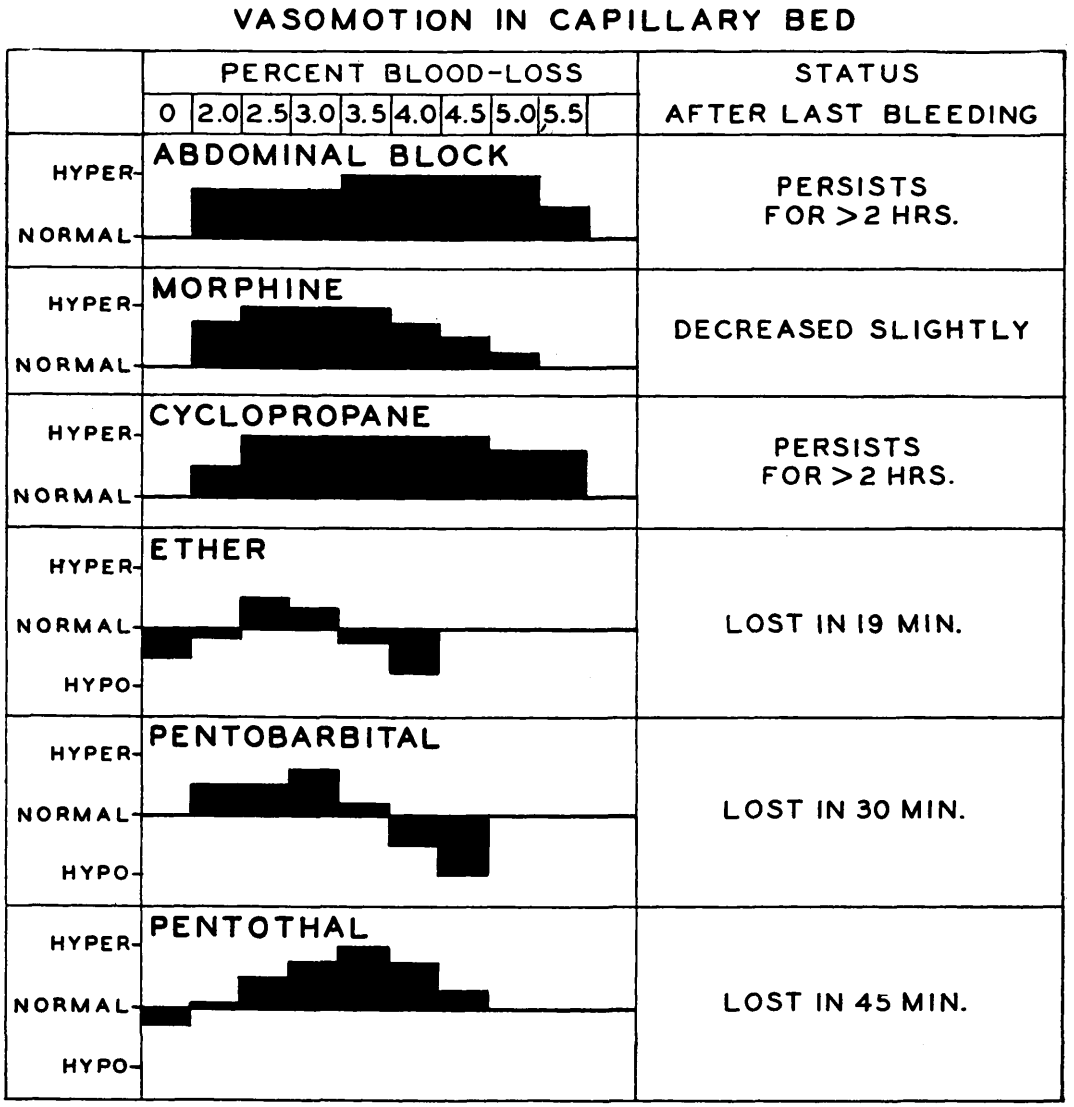

FIG. 2.

hemorrhage induced a compensatory restriction of the capillary circulation. This restriction appeared as an ischemic state in which the flow became confined to certain channels in the bed. The time of the appearance of this state and its duration are indicated in Fig. 1 by the symbol "R" below the graphs representing rate of blood flow. The loss of this compensatory reaction appeared as a state in which the blood flow, though deficient, spread throughout the entire capillary network. This unrestricted state is represented in the figure by the symbol "U." Loss of this compensatory mechanism was observed during ether, pentobarbital, and pentothal anesthesia and not with the other agents.

Vasomotion. As has been reported previously,[1] hemorrhage invariably results in the development of an increased vasomotion in the muscular channels of the capillary bed. The restriction of capillary flow was found to occur only during the period when the increased vasomotion was maintained. Loss of this activity was always accompanied by a filling of the entire capillary network and a marked decrease in the venular outflow.

Fig. 2 illustrates the changes in vasomotion following bleeding during the different anes-

TABLE III.
Epinephrine Reactivity of Omental Vessels Following Hemorrhage.

% Blood-Loss	0	2	2.5	3	3.5	4	4.5	5	5.5	Status after last bleeding
Abdominal Field Block	1x	2.2x	—	3.3x	4x	4x	5x	6x	10x	Persists high for >2 hr
Morphine	1x	1.5x	2.0x	2.2x	3.0x	3.5x	4.8x	5.8x	6.3x	Decreases only slightly in 90 min
Cyclopropane	1x	2x	2.5x	7.3x	10.6x	14.9x	14.2x	15.9x	13.3x	Persists high for >2 hr
Ether	1x	1.8x	2.1x	5.9x	5.5x	7.2x				Decreases markedly in 54 min
Pentobarbital	1x	1.6x	2x	2.2x	2.3x	2.5x				" " " 45 "
Pentothal	1x	2.5x	4.6x	5.6x	8.8x	9.3x	14.2x			" " " 73 "

Changes in epinephrine reactivity are indicated as multiples of the normal values prior to bleeding which are designated as 1x.

thetic procedures. Ether and pentothal, as compared with the control, dampened this activity even prior to hemorrhage. Following blood-loss during ether, pentobarbital, and pentothal anesthesia, the vasomotion progressively fell to hyponormal levels and was completely lost approximately 20 to 45 minutes after the final bleeding. In the controls and those receiving cyclopropane, a hypernormal condition was evident soon after the onset of hemorrhage and was maintained throughout the period of observation. Those receiving morphine resembled the control series except that the vasomotion slowed slightly during the final two bleedings.

Epinephrine Reactivity. The minimal effective concentration of epinephrine was determined for each dog prior to bleeding by applying the drug to the surface of the omentum and noting the concentration which produced a narrowing of the metarterioles[3] just sufficient to slow the capillary flow. In the controls, shortly after the initial bleeding there was a progressive increase in this reactivity (see Table III). With cyclopropane and pentothal anesthesia, the initial values, prior to hemorrhage, were higher than those of the control group. Despite this they showed the greatest increase in reactivity to epinephrine following hemorrhage. With pentothal, however, a marked decrease in this response occurred within 75 minutes after the final bleeding, in contrast to the cyclopropane group, in which this activity was maintained throughout. Those receiving ether or pentobarbital showed a rapid loss of post-hemorrhagic hyper-reactivity following the last bleedings. The dogs given morphine closely resembled the controls except that their response following bleeding increased only 6x as compared with 10x in the controls.

Summary and Conclusions. 1. Circulatory responses to graded hemorrhage varied significantly with six anesthetic procedures studied. 2. Of the drugs studied with the criteria used, the changes with cyclopropane most nearly approached those observed in animals receiving only local procaine. 3. The effects of anesthetic drugs must be taken into consideration in evaluating experimental shock studies.