STUDIES IN INACCESSIBLE INTERNAL HEMORRHAGES*

I. THE EFFECT OF ADRENALIN ON INTESTINAL HEMORRHAGE

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I. INTRODUCTION

From a therapeutic point of view hemorrhages may be classified as *accessible*, i. e., those that can be directly influenced by drugs and *inaccessible*, i. e., those that can be influenced by drugs only through the circulation. In the former class come hemorrhages from the mouth, nose, throat, eye, wounds, etc., and such internal hemorrhages as can be reached by topical applications, viz., those from the uterus, urethra, bladder, stomach, rectum, etc. In the latter class may be listed intestinal, pulmonary, renal, uterine and cerebral hemorrhages.

The value of adrenalin in accessible hemorrhages is well recognized, but so far its use in inaccessible hemorrhages has been condemned rather than commended by our best therapeutists. The chief reason for this is the fact that adrenalin, when introduced into the vascular system, not only causes an active constriction at the point of bleeding, but also raises the blood pressure by a general constriction which tends passively to counteract the local influence and so augment bleeding. For this reason drugs that cause a fall of blood pressure have been recommended on the supposition that the pressure change would more than balance the local dilatation and so favor coagulation.

Unfortunately such a plan of treatment can not always be safely instituted. If the hemorrhage has already been profuse and the blood pressure is consequently low, or, if the hemorrhage is accompanied, as in surgical cases, by varying degrees of shock, it would be unwise therapeutics to lower the blood pressure still further; for it is as vital that the medullary centers should be sufficiently supplied with blood as it is important that the hemorrhage should be checked. In such cases it is necessary that the greatest portion of the remaining red blood corpuscles should be diverted from the channels where they are less needed, to the brain, where their presence is urgently demanded. The injection of saline solution accomplishes this only imperfectly, for the augmentation in pressure occa-

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sioned by the increased volume is counteracted by the dilution of hemoglobin and the tendency to increased bleeding.

In precisely such vascular disturbances, when unaccompanied by hemorrhage, as in shock, it has been found that adrenalin accomplishes this better than any other drug. It is only the empirical assumption that it always causes an unfavorable increase in hemorrhage that prevents the use of what otherwise would be the drug of choice in hemorrhages accompanied by vascular failure.

Recent researches, however, have demonstrated reactions of blood vessels to adrenalin which caused prominent men to abandon this view and even advocate its use in such cases^{1, 2}.

II. REACTIONS SUGGESTING THE USE OF ADRENALIN

1. It has become a well substantiated fact that the reaction of normal blood vessels to adrenalin is of very brief duration. It is found, however, that the same dose which produces such a fleeting rise of pressure in a living animal causes a prolonged reaction when tested on a perfused organ from the same animal. The investigations of Meltzer showed that a prolonged reaction was also obtained in the body if the nerve supply to the vessels was cut. He¹ assumed that adrenalin affected blood vessels not only by a peripheral constriction, but that this tended to be neutralized and shortened by a central dilator action. When this central influence was interfered with in any way the peripheral constriction persisted for a longer time.

Application.—Assuming with Meltzer that the pathological process which caused the hemorrhage has also interfered with the nerve supply of the portion adjacent, it may be expected that the contraction at the point of injury will outlast the general rise of pressure and so tend to favor cessation of the bleeding.

2. It has been well demonstrated by perfusion experiments that the vessels of all regions of the body do not react equally to adrenalin. In some regions, as the intestines and kidney, its local action is great enough to counteract a considerable rise in pressure, but in other regions, as the brain, any local action is immediately overpowered by a small rise in pressure³.

Application.—It appears not unlikely that whole sets of vessels in regions susceptible to adrenalin may divert, by their contraction, the flow of blood to other regions less affected. Thus, in spite of a slight pressure rise, the flow of blood from ruptured vessels may lessen.

1. Meltzer (S. J. and C.): Am. Jour. Physiol., 1903, ix, 260.

2. Schaefer: Brit. Med. Jour., 1908, ii, 1350.

3. Wiggers: Am. Jour. Physiol., 1905, xiv, 452; 1907, xx, 106.

3. The effect of adrenalin on blood pressure is determined by the strength of solution, as well as by the rate and method of introduction into the body. It is possible, for example, to introduce adrenalin intravenously in such weak solutions that the pressure rises only very slightly, or it may be introduced continuously so that this slight rise remains permanent⁴. Meltzer reported that given subcutaneously it caused either a slight rise or slight fall in pressure,⁵ while given intramuscularly the rise of pressure occasioned was more prolonged though not so high as when given intravenously, and the fall was more gradual.

Application.—It is evident that the classical great and sudden rise of pressure of short duration which is immediately suggested by the use of adrenalin need not occur. In fact, the use of such doses is experimental, not therapeutical.

4. Adrenalin is reputed to increase the coagulability of the blood⁶. The application of this observation in facilitating clot formation need not be explained.

III. PREVIOUS WORK ON INTESTINAL HEMORRHAGE

The value of adrenalin in inaccessible intestinal hemorrhages has not been the subject of many direct experiments. Lisin⁷ recently investigated the subject experimentally. This worker rendered the blood of dogs non-coagulable by the injection of peptone, then created intestinal hemorrhages and estimated the degree of hemorrhages from time to time by determining the quantity of hemoglobin lost in definite time intervals. As a result of these studies he reported that intravenous injections of rather large doses of adrenalin caused a rapid and often instantaneous hemostasis, one that coincided with the rise in pressure and remained permanent after its fall.

Aside from the facts that the accuracy of the method of estimating the degree of hemorrhage is questionable,⁸ and that the use of peptone causes severe circulatory disturbances, his research is open to a very practical criticism. He concludes: "Adrenalin does not really prove a hemostatic unless the vasoconstriction is accompanied by considerable slowing of the heart." Now it is well known that doses of adrenalin large enough to slow the heart act also to cause a cessation of respiration during the interval of action. Such doses when administered to patients have given

4. Kretchmer: Arch. f. exper. Path. u. Pharmacol., 1907, lvii, 423.

5. Meltzer and Auer: Jour. Exper. Med., 1905, vii, 59; Am. Med., 1905, ix, 75.

6. Vosburgh and Richards: Am. Jour. Physiol., 1903, ix, 39.

7. Lisin: Arch. internat. de pharmacod. et de therap., 1907, xvii, 465.

8. Wiggers: Am. Jour. Physiol., 1908, xxiii, 23.

rise to alarming symptoms, and in several instances to pulmonary edema. It is clear that these doses can never become practical in therapeutics.

This research was undertaken to test the influence of adrenalin in doses small enough not to affect either the rate of the heart or respiration.

IV. APPARATUS AND TECHNIC EMPLOYED IN THIS RESEARCH

In this research hemorrhages were created and changes in the outflow of blood recorded by a special form of apparatus, which did not necessitate the defibrination of blood and hence avoided the establishment of

Fig. 1.—Diagram of hemorrhage-collecting apparatus. Letters referred to in text: H, a time signal; K and L, two stops, limiting the excursion of the aluminum beam C to range of drum.

abnormal conditions which such a process entails. The hemorrhage recording device (diagrammatically shown in Figure 1) has recently been described in detail⁶. As blood dripping from the wounded vessels above the apparatus is received into the dripping collecting pan (D) it causes the aluminum beam (C) on the other side of a knife edge (A) to rise and record on a smoked drum by a celluloid pointer (F) moving in a horizontal axis set in the end of a lever. When the lever has reached the top of the smoked paper the drip pan is emptied and another record started. On an evenly moving drum the pointer writes an oblique line

which becomes more inclined to the vertical or horizontal as hemorrhage increases or decreases (see subsequent curves). The apparatus is calibrated so that the actual quantity of blood lost can be estimated mathematically for definite time intervals. It possesses the further advantage that these intervals can be so chosen that outflow changes are not obscured.

Dogs were anesthetized as lightly as possible with morphin and chloretone dissolved in 40 per cent. alcohol. Canulæ were then inserted into the carotid artery and femoral or jugular veins. A small medium abdominal incision was made and a loop of small intestine with its mesentery was brought from the abdomen. With the intestine protected as much as possible by warm gauze sponges, silk ligatures were placed in loose loops around the mesenteric vessels as they passed toward the intestine. This completed, the intestines and mesentery, with the exception of the small portion where ligatures had been placed, were protected by gauze and the whole abdomen was surrounded by a rubber bandage. In the latter an opening was cut so as to expose the isolated vessels. The dog, with abdomen down, was then suspended in a hammock arrangement above the drip-recording apparatus before described. When the carotid pressure and respiration were being satisfactorily recorded, a mesenteric vessel was cut and the blood received in the drip pan and recorded.

V. THE NATURAL COURSE OF ARTERIAL INTESTINAL HEMORRHAGE

In a study of the natural course pursued by an arterial intestinal hemorrhage attention was attracted to the fact that the initial amount of blood leaving the vascular system was not entirely dependent on the diameter of the vessels wounded, but varied rather in accordance with the product of this diameter and the pressure existing at that time. Thus the flow from a small artery could be as great as that from a larger one. From the time of its inception to its final cessation the bleeding diminished gradually, but more rapidly at the beginning than toward the end of its course, so that a plotted curve appears more or less concave to the abscissæ.

Comparisons of hemorrhages from various sized vessels (Fig. 2) show, furthermore, that the early diminution was much more rapid in hemorrhages from large vessels than in those from smaller ones, with the result that about three minutes after its beginning the flow from the larger and smaller arteries became nearly equal. This was due to the fact that the greater outpour of blood from the larger vessels not only caused the pressure to fall more rapidly, but also afforded increased material to favor clot formation over the wound.

The time elapsing before cessation finally occurred varied considerably. Sometimes the hemorrhage was checked within a few minutes with little fall in blood pressure. At other times it continued, as in the case of the experiment plotted in Figure 3, until the pressure became very low or death supervened. Experiments soon showed that this variation

Fig. 2.—Three plots from Experiments 3, 10 and 4 respectively, showing the characteristic diminution of hemorrhage from large and small vessels.

in duration depended, not so much on the size of the vessel wounded, nor on the fall in pressure, as on the facility with which a clot formed over the wound. Observation of the process of clotting around a wounded vessel showed that blood flowing from a wounded artery does not begin to coagulate immediately at the point of hemorrhage, but on the tissues

Fig. 3.—Plot from Experiment 1, June 24, 1908, showing effect of progressive hemorrhage on blood pressure..

at a distance. After an adherent clot had been formed there it was added to progressively until it reached and covered the source of hemorrhage. Then hemorrhage was checked. If the surface over which the blood could spread by gravity or other forces was great, the first clot formation occurred at a greater distance from the wounded vessel than if the

space over which it could flow was circumscribed in some way to the locality of the bleeding. With the technic employed the coagulating surface varied considerably in different experiments. Sometimes the mesentery was smoothly stretched, at other times gathered into folds with depressions between them. Sometimes the vessel was at the bottom, at other times at the summit of such a fold. This lack of uniformity was the cause of the varied duration of hemorrhages. One of the chief reasons that gastric and intestinal hemorrhages are not more frequently fatal is that the ulceration which causes the hemorrhage also supplies a mechanism for its rapid checking; viz., an excavation limiting the spread of blood.

VI. THE INFLUENCE OF ADRENALIN ON INTESTINAL HEMORRHAGES

After hemorrhage had progressed for intervals of time ranging from one to twenty minutes, adrenalin made up in solutions varying in strength

Fig. 4.—Scheme to illustrate the influence of adrenalin on the natural course of an intestinal hemorrhage. Description in text.

from 1 to 20,000 to 1 to 200,000 was injected in doses containing from 0.01 to 0.2 mg. (1/6400 to 1/320 grain).

The results of these injections show that, under favorable conditions, the dose of adrenalin determines the effect on the course of hemorrhage much in the manner diagrammatically expressed in Figure 4. Every hemorrhage, as expressed by the arc AB, has a natural tendency to diminish and cease. A dose of adrenalin so small as to produce no effect may be administered during the course of the hemorrhage. The quantities from which the first effects are noticed undoubtedly cause a slight further diminution directly after injection. This shortens the course, as may be expressed by the arc M. As the dose of adrenalin is increased the dimin-

ution of hemorrhage seen is preceded by a temporary increase which, as larger doses are used up to a certain limit, becomes more and more pronounced. The diminution following the increase also becomes more pronounced and prompt after each larger dose, so that, though the injection is immediately followed by an even greater loss of blood, the course is actually shortened (arc N or O). A dose is finally reached which causes no greater preliminary increase, but after which the diminution or cessation is equally prompt and certain. These results are illustrated by the curves shown in Figures 5, 6 and 7.

1. *Cause of the Preliminary Increase.*—Comparisons of the blood pressure records with those indicating the degree of hemorrhage show that the rise of blood pressure is responsible for the preliminary increase in the loss of blood. When only a slight rise of blood pressure is occasioned (Fig. 5) the local action of adrenalin on the wounded intes-

Fig. 5.—Segment of a record from Experiment 37, Aug. 7, 1908, showing the effect of a dose of adrenalin too small to cause an increase in hemorrhage, but large enough to cause a subsequent decrease. Blood rendered non-coagulable in this experiment. R, respiration; B P, blood pressure; T, time in intervals of 10 seconds, written on the base line for the present record; H, degree of hemorrhage recorded by hemorrhage-recording apparatus. Hemorrhage-recording apparatus wrote 4 mm. to the left of blood-pressure pointer. In all records of respiration the down-stroke represents inspiration, the up-stroke expiration. Adrenalin, 0.025 mg.

tinal vessels can apparently counteract it, but this local action does not increase proportionally with the rise in pressure, so, as the latter becomes greater, the preliminary increase follows (Fig. 6). The fact that extremely large doses cause no greater preliminary hemorrhage than smaller doses is explained by the fact that large doses slow the heart exceedingly, which keeps the pressure from exceeding a certain limit.

In dogs 0.01 to 0.025 mg. of adrenalin usually produced a satisfactory decrease in hemorrhage, while the preliminary increase in pressure

was so slight that, if any increase of flow preceded the decrease, it was very slight and transient. (Compare the rise of pressure and increase in outflow in Sections A and B, Table 1). Inspection of the preliminary increase occasioned in the experiments listed in Section C of this table will show, however, that this was not invariably slight and unimportant. This was because other factors than the actual dose must be taken into consideration in the administration of adrenalin.

A. The Variable Reaction of Animals to Adrenalin: Although the same dose of adrenalin causes practically the same relative rise in pres-

TABLE 1*

Experiment.	Initial Outflow per 20 sec.	Dose of Adr.	Interval before Injection.	Diastolic. Blood Pressure			Actual Rise in Pressure.	Outflow of Blood per 20 Sec.			Preliminary In- crease, Actual.	Subsequent De- crease, Actual.
				Before.	During.	After.		Before.	During.	After.		
	c.c.	mg.	min.	mm.	mm.	mm.	mm.	c.c.	c.c.	c.c.	c.c.	c.c.
9A	5.8	.025	2½	32	36	32	4	2.3	2.9	2.4	.6	0
.....	5.8	.025	4	32	36	32	4	2.4	2.5	1.9	.1	.5 A
12B	3.6	.025	3¾	37	42	38	5	2.4	2.9	1.4	.1	1.0
9A	5.8	.025	7	30	37	30	7	.9	.7	0	0	.9
20C	5.4	.025	3	33	40	32	7	4.8	5.4	1.0	.6	3.8
9B	4.2	.025	1	12	20	11	8	4.2	4.6	3.0	.4	1.2
.....	4.2	.025	3	12	20	10	8	2.9	3.0	1.9	.1	1.0
12B	3.6	.025	14	35	46	38	11	1.5	2.5	1.0	1.0	.5
7C	1.5	.025	2	52	70	56	18	1.0	1.0	.7	0	.3 B
18A	5.4	.025	2½	56	70	54	14	3.7	3.9	.3	.2	3.4
7A	1.2	.025	3¾	54	86	54	34	1.3	1.9	.3	.5	1.0
7B	.9	.025	14	62	90	65	23	1.2	2.0	0	.3	1.2
12A	10.0	.020	5	64	70	64	6	5.2	6.7	4.7	1.5	.5
18B	6.5	.025	2½	48	60	44	12	2.2	5.4	.9	3.2	1.3
7D	1.1	.020	6	37	48	41	11	1.4	3.0	2.9	1.6	1.0 C
18B	6.5	.025	1½	48	74	42	26	4.2	8.7	2.2	4.5	2.0
19B	8.8	.025	11	38	72	35	34	8.0	5.0	2.0	2.0	1.0
19B	8.8	.050	5½	46	94	46	48	4.4	8.0	2.7	3.6	1.7
6B	3.0	.080	6	30	90	36	60	.2	1.9	0	1.7	.2
6D	0.8	.10	11	22	64	26	42	.1	.3	.1	.2	0 D
6E	0.6	.20	15	22	54	23	32	.2	.8	.1	.6	.1

*The data comprised in this table have been selected as representative of a table listing the results of forty injections of adrenalin.

sure after each subsequent injection into the same animal, it is unfortunate that no such constant relation between dose and degree of reaction exists between various animals. It may be added that in these experiments care was taken to insure accurate dosage. Deterioration of the adrenalin solution was avoided by dissolving just before use a tablet triturate of adrenalin in the requisite amount of salt solution, and all injections were made with a graduated syringe after first filling the canula and connections with the adrenalin solution. Under these con-

ditions it was found that 0.025 mg. might cause any elevation of pressure between 4 and 34 mm. of mercury. (Compare Sections A, B and C of Table 1). It is not the purpose of this article to delve into the causes of this varied susceptibility of animals to adrenalin. It is merely necessary to point out the fact that human beings, as well as animals, may vary in their susceptibility. Thus reserve and caution demand that in the practical use of adrenalin not too much reliance should be placed on a definite dose and that its therapeutic use, for the present at least, should be accompanied by careful blood pressure observations.

Since such great variation in pressure results from a certain dose, corresponding variations must be expected in the preliminary increase of hemorrhage.

B. The Quantity of Blood Lost Before Administration of Adrenalin: The suggestion naturally arises that the amount of blood lost before

Fig. 6.—Segment of a record from Experiment 29, July 30, 1908, showing effect of a dose of adrenalin sufficient to cause a preliminary increase. The subsequent decrease occurs in several stages, A, B and C referred to in text. Lettering otherwise same as before. 1 c.c. = 4 mm. vertical rise.

adrenalin is administered may determine the degree of the preliminary increase. For example, it may be argued that, after a progressive loss of blood and a consequent lowering of pressure, adrenalin can not cause as great an increase of pressure as when injected while the pressure is higher. This is an important point to determine experimentally, for it leads to the assumption that larger doses may be employed when the pressure is low without incurring the risk of a greater preliminary increase. A comparison of the data, in heavy type, of Section B, Table 1, shows that, though small doses injected after much blood had been lost and the

pressure was consequently low, did not cause as great an increase in pressure as they did when injected early in an experiment while the pressure was still high, they exerted the same effect on the preliminary increase of hemorrhage. (Compare Experiment 9 B, 12 B, with Experiment 7 A, B, C, and 18 C). On the other hand, it was found that a large dose, for instance, 1 mg., induced a greater flow if given after hemorrhage had progressed for some time than if administered early (Fig. 8). This happened because the high pressure produced was powerful enough to dislodge the clot which had gradually formed and which was contributing to the checking of the hemorrhage.

Fig. 7.—Segment of a record from Experiment 27, July 29, 1908. Effect of a large dose of adrenalin on pressure and hemorrhage. Lettering same as before. Adrenalin .05 mg.

The practical conclusion may then be emphasized that large doses must not be employed for fear of dislodging clots and thus seriously increasing hemorrhage. The slight rise of pressure caused by smaller doses is not powerful enough to dislodge the clot and they are therefore indicated late as well as early in the course of hemorrhage.

C. The Size of the Hemorrhage: Simple reasoning tells that a certain rise of pressure will cause a greater efflux of blood from a large than a small vessel, and so adrenalin seems fraught with greater danger in the larger hemorrhages. Experiments showed that while this is often

so it can be obviated to a great extent by a judicious choice of the time of injection (Section C, Table 1). As was previously pointed out, the amount of blood lost from large vessels is, within a few minutes after starting, no greater than from small ones, for the pressure in the former falls more rapidly and the opening is more speedily occluded by a clot than in a smaller vessel in which the pressure remains higher. Now, if a dose of adrenalin is injected early in the course of a hemorrhage, before this diminution has taken place it will cause a greater preliminary increase than a similar dose would from a smaller vessel. If, however, one waits with the injection until a diminution occurs, the absolute increase accompanying the injection is no greater than from a smaller vessel, provided the dose does not cause too great a rise of pressure. It seems reasonable to assume that by the time an injection can be given to a patient, the hemorrhage will, if from a large vessel, have diminished sufficiently so that its administration is not beset with excessive danger.

Fig. 8.—Plot from results of Experiment 12, July 9, 1908, showing relative effects of a large dose before and after formation of a coagulum over wounded vessel. Lettering same as before.

2. *Cause of the Subsequent Decrease.*—Following the preliminary increase of hemorrhage observed in forty experiments, adrenalin was found to cause an immediate cessation in 40 per cent. of injections, a marked decrease in 47 per cent., while in 13 per cent. no favorable action followed. It remains to analyze the causes of this subsequent decrease or cessation.

Figure 6 shows well the nature of those experiments in which cessation followed the use of adrenalin. Careful inspection of the record shows that this cessation occurred in two stages. After the increase of hemorrhage at A, a marked reduction below the normal followed instantly at B. This was followed by a final change to a cessation at C. In

other experiments the reduction at B was the same, but the final cessation at C was absent.

The first diminution was not due to the lowered pressure following the injection of adrenalin, as may be argued from the appearance of Figure 6, for it was more usual for the pressure not to be lower. It could also not be explained as a dynamic effect from the loss of blood for the following reasons:

1. Occasionally the diminution was absent after a preliminary increase (Experiment 9 A, 7 D), and again it was present when no preliminary increase had occurred (7 C, 18 A).

2. If the pressure and hemorrhage were augmented by stimulating the sciatic, the preliminary increase was occasioned by an elevation of pressure, but the subsequent decrease was absent.

The assumption then seems warranted that adrenalin acts longer at the point of injury than on the general blood pressure. This prolonged constriction caused the decrease in hemorrhage at B and this in turn favored clot formation, which caused the final cessation of hemorrhage at C. When adrenalin merely reduced but did not absolutely check hemorrhage, conditions for coagulation were not favorable around the opening. In order not to make this assertion without corroborating evidence several confirmatory tests were made.

In one series of check experiments the original technic of preparing the mesenteric arteries was retained, but the animal's blood was rendered non-coagulable by withdrawing at half-hour intervals a part of its blood, defibrinating it, and, after warming, reinjecting it into the jugular vein. In these cases hemorrhage diminished only as the pressure fell and cessation occurred only at the death of the animal. Adrenalin caused the same preliminary increase in hemorrhage followed by a decrease, but never by a cessation (Fig. 5).

In another series of cases the clot formation was interfered with by isolating each mesenteric vessel, doubly ligating it and cutting between the ligatures. To a short ligature left attached to the proximal end of an artery a light weight was attached, so as to place the vessel under a slight tension and draw it away from the mesentery. A lateral incision was then made in the vessel, as a result of which the blood passed down the thread in a pulsating spiral stream and dropped without touching the surrounding tissue. In this case the clot started to form at the place where the ligature was tied to the vessel, but the tendency for the clot to build up was counteracted by the downstreaming of blood. Adrenalin, administered under these conditions, practically reduplicated the curve shown in Figure 5. Absolute cessation never followed.

We may then conclude that adrenalin, by narrowing the lumen of blood vessels, can diminish hemorrhage after the rise of pressure has passed off. There is no proof that adrenalin can itself completely obliterate the vessels, however. The coagulating property of the blood is necessary to complete the action of adrenalin.

In regard to the 13 per cent. of cases in which adrenalin failed to diminish hemorrhage, it may be said that out of the five cases in which this occurred, in two (Experiments 6D, 6E, Table 1) the adrenalin was administered so late that the hemorrhage had already nearly ceased and hence no benefit could occur.

A. The Effect of Adrenalin on Coagulation of Blood: The question arises in this connection whether adrenalin also aids by actually hastening the coagulation of the blood. The frequent coagulation of blood in the canulæ during adrenalin experiments has been attributed to this factor by certain pharmacologists. The only research bearing on the problem was that of Richards and Vosburgh⁶. These workers report five experiments (one of which is absolutely negative) from which they conclude that adrenalin shortens the coagulation time as a result of its application to the pancreas.

The question was not extensively studied in this research and no permanent conclusions will be drawn. It may be stated, however, that as a result of many tests made on five dogs there was never the slightest indication that adrenalin, either when injected or added to the blood, appreciably hastened the coagulation process. A typical experiment is appended.

EXPERIMENT.—Aug. 20, 1908. Dog, anesthetized with morphin and chloretone. Carotid artery, jugular vein and femoral artery prepared and canulæ inserted into each, a very short one in the latter. After each test, the canula in the femoral artery from which blood was drawn was rinsed with salt solution and dried with cotton swabs. For each test 1 c.c. of blood was drawn into a short test-tube, 7 mm. in diameter, and the time until the tube could be inverted without spilling, recorded. The observations follow:

Time.	Coag. Time.		Time.	Coag. Time.	
10:08.....	3.25 min.		10:40.....	Adr. 5 c.c.	1:100,000
10:11.....	2.75 min.		10:42.....	2.00 min.	
10:14.....	3.00 min.		10:45.....	3.00 min.	
10:18.....	3.00 min.		10:53.....	Adr. 5 c.c.	1:100,000
10:23.....	3.25 min.	4 gtt. Salt	10:54.....	3.00 min.	
	3.25 min.	4 gtt. Adr.	10:55.....	2.50 min.	
10:27.....	3.25 min.	4 gtt. Salt	11:00.....	3.00 min.	
	3.25 min.	4 gtt. Adr.	11:02.....	2.25 min.	
10:32.....	3.00 min.	4 gtt. Salt	11:05.....	3.00 min.	
	2.75 min.	4 gtt. Adr.	11:08.....	Adr. 5 c.c.	1:100,000
10:36.....	3.00 min.	4 gtt. Salt	11:09.....	2.75 min.	
	3.25 min.	4 gtt. Adr.	11:12.....	2.75 min.	

3. *The Value of Other Modes of Administration.*—The different methods of introducing adrenalin were investigated with the hope that perhaps the unfavorable preliminary increase in hemorrhage due to the high pressure occasioned could be eliminated or minimized, while the favorable decrease could still be retained.

A. Continuous Intravenous Injections: To produce continuous intravenous injections of adrenalin the solution was placed in a graduated burette and this was connected with the femoral vein. The rate of inflow was regulated by a clamp with a fine screw thread placed on the connecting tube, so that quantities of adrenalin from 0.06 to 0.005 mg. were introduced per minute.

TABLE 2.

Exp.	Rate of Injection per min. mg.	Duration of Injection min.	Effect on Pressure During Injection.	—Effect on Hemorrhage.— During. After.	
15A	.066	½	Rise 33	Marked Increase.	Cessation.
15C	.056	1 ½	Rise 20<62>22	Marked Increase.	Cessation.
15B	.04	3	Rise 22<28>12	Increase sl. Decrease.	Cessation.
15D	.028	3 ½	Rise 12>6	Increase.	Cessation.
15A	.02	4	Rise 15>6	Temporary Increase. Decrease.	Further Decrease.
15E	.018	3 ½	Rise 0>2	Decrease.	Decrease.
8B	.01	7	No change	Decrease.	Decrease.
25A	.008	4	Rise 4>0<2	Decrease.	Decrease.
25B	.008	4	Rise 5>3	Sl. increase Decrease.	Cessation.
25C	.007	4 ½	Rise 4>0<2	Decrease.	Decrease.

> means decreased to.
< means increased to.

A glance at the results shown in Table 2 indicates that the doses of adrenalin exceeding 0.02 mg. per minute caused a considerable rise in pressure, which occasioned an increased flow as long as the introduction lasted. A great diminution or cessation of hemorrhage followed as soon as the injection ceased. Evidently the continuous administration of large doses possessed no advantage over instantaneous injections, while it had the disadvantage that the increase in hemorrhage was prolonged, whereas the real aim is to reduce the duration of the increase as much as possible.

Smaller amounts injected continuously during a definite time (0.007 to 0.01 mg. per minute) caused very little rise in pressure and little or

no preliminary increase in hemorrhage (Fig. 9). The diminution following compared favorably with that following single injections. The method of continuous administration is preferable in cases of hemorrhage accompanied by great vascular failure. In these it becomes of greater importance to maintain a higher pressure than to check hemorrhage quickly, and the fact that this can be done by adrenalin without augmenting hemorrhage is of great practical advantage.

B. Subcutaneous Injections: This method of administration was tested, but with negative results as far as the effect on blood pressure and hemorrhage were concerned. The reactions reported by Meltzer on rabbits could not be obtained in these experiments on dogs. It seems

Fig. 9.—Segment of record from Experiment 25, July 27, 1908, showing effect of a continuous intravenous injection of adrenalin (1 to 300,000 at rate indicated on curve) on hemorrhage and blood pressure. Lettering as before.

certain, at least, that by this method not enough adrenalin enters the circulation to act efficiently on the blood vessels.

C. Intramuscular Injections: By deep intramuscular injections it is possible to introduce a desirable quantity of adrenalin into the blood stream. Seven experiments were made to determine the effect of adrenalin on intestinal hemorrhage when administered in this way. In each case from 0.5 to 5 c.c. of a 1 to 1,000 adrenalin solution was injected into the pectoral or dorsal muscles. The effect on hemorrhage much resembled that observed in continuous intravenous injections except, as

shown in Figure 10, the increase occasioned by the rise was converted into a decrease before the pressure fell. This occurred every time, even when a great rise in pressure followed an intramuscular injection. These favorable results and the convenience of the method favor its employment when hemorrhage is to be checked and the pressure increased. Larger doses are required when this method is used. In dogs 1 mg. given intramuscularly induces no greater effect on hemorrhage than 0.025 mg. given intravenously.

VII. THE EFFECTS OF NITRITES ON INTESTINAL HEMORRHAGE

Seventeen injections of nitrites were made during various stages of hemorrhage in order that their use might be compared with that of

Fig. 10.—Segment of a record from Experiment 56, Aug. 27, 1908. Effect of an intramuscular dose of adrenalin on blood pressure and hemorrhage. Lettering as before. 1 c.c. adrenalin 1-4,000 intramuscular.

adrenalin. The results following the inhalation of amyl nitrite and the intravenous injection of nitroglycerin and sodium nitrite are incorporated in Table 3. Usually the nitrites caused an immediate fall of pressure, which was somewhat slower after inhalation of amyl nitrite than after the introduction of the others. In the case of amyl nitrite and nitroglycerin the fall was temporary, the pressure gradually returning to normal again, but in the case of sodium nitrite it remained low. The degree to which the pressure fell depended largely on the dose. The actual height of the pressure did not influence the relative fall.

In 76 per cent. of cases the fall of pressure caused an immediate diminution of hemorrhage. In 40 per cent. of these cases this was followed by a total cessation, even when the pressure returned again to normal; in 30 per cent. a further decrease occurred; while in another 30 per cent. the flow increased again to normal or above normal. When a total cessation or marked diminution occurred it was due to the fact that coagulation was favored by the lowered pressure; but when no such change took place the conditions for coagulation were unfavorable. A subsequent increase occurred only when the pressure returned to normal and a clot had not formed over the vessel. Even then hemorrhage had been temporarily benefited.

TABLE 3.

Experiment.	Drugs and Dose.	Initial Outflow per 20 sec.	Interval before Injection.	Diastolic Blood Pressure			Fall in Pressure.	Outflow of Blood per 20 sec.		
				Before.	During.	After.		Before.	During.	After.
	Amyl nitrite.	c.c.	min.	mm.	mm.	mm.	P.C.	c.c.	c.c.	c.c.
6C	5 gtt.	2.9	7	26	23	26	11	.7	.5	.8
47A	10 gtt.	21.0	2½	72	54	70	25	15.0	6.8	0
57A	5 gtt.	7.5	4	50	47	48	6	4.0	2.0	0
*58C	5 gtt.	3.0	12	28	23	25	17	3.0	3.0	2.25
....	3 gtt.	7.0	7½	32	25	30	25	2.5	.7	.2
Nitroglycerine.										
33	1/250 gr.	3.7	5	100	70	90	30	3.3	2.5	1.0
...	1/100 gr.	3.7	12	84	56	79	32	1.0	0	0
34B	1/100 gr.	23.7	8	56	38	52	32	7.5	7.7	5.0
47B	1/100 gr.	23.6	3½	50	34	49	29	8.3	7.2	0
50C	1/100 gr.	18.0	2	22	6	18	72	14.0	4.3	0
24B	1/100 gr.	6.4	2	22	15	22	31	6.0	2.0	1.4
Sodium Nitrite.										
54	2¼ gr.	16.0	3¼	54	22	22	60	11.8	4.5	2.3
...	2½ gr.	16.0	12	22	18	18	13	2.0	1.5	1.5
*57C	3 gr.	3.0	9	22	14	14	36	2.0	0.5	.5
47D	15 gr.	14.0	2½	28	16	16	57	13.0	.75	.75
48	10 gr.	11.2	6½	92	33	33	64	2.0	1.5	3.0
49A	10 gr.	5.0	3	56	26	26	53	1.6	.5	.2

* Blood rendered non-coagulable.

In 24 per cent. of cases the fall of pressure had no beneficial effect on hemorrhage. In two of these cases (Experiments 34 B, 47 B) the hemorrhage was from a very large vessel, and in the other cases the pressure had already been permanently lowered by previous administration of nitrites, so that subsequent injections caused only a slight fall.

It may be concluded, then, that nitrites, by the fall in pressure induced, cause an immediate diminution of hemorrhage, followed by cessation, if conditions for coagulation around the wound are favorable.

There is, however, a danger in lowering the pressure by the use of nitrites in cases in which hemorrhage has continued for long intervals of

time. This danger is not theoretical, but can be experimentally demonstrated. In three experiments after the pressure due to hemorrhage had become very low an injection of nitrites was made, which, by its fall in pressure, caused not only a diminution of hemorrhage, but also a failure of the respiration and the heart.

VIII. CONCLUSIONS

The following conclusions may be drawn regarding the use of adrenalin in intestinal hemorrhages:

1. Large doses of adrenalin (0.05 to 0.1 mg.) cause a short preliminary increase in hemorrhage followed quickly by a decrease or cessation

Fig. 11.—Segment of record from Experiment 57, Aug. 28, 1908. Effect of nitrites on blood pressure and hemorrhage. $2\frac{1}{2}$ grains NaNO_2 .

of bleeding. On account of the great preliminary loss of blood they are always contraindicated.

2. Small doses of adrenalin (0.01 to 0.025 mg.) cause little or no preliminary increase, but shorten the course of hemorrhage. As they save the red blood cells in every way they are therapeutically desirable.

3. The method of introducing adrenalin determines the effect on blood pressure and hemorrhage. No results are obtained by subcutaneous administration. By continuous intravenous injection of weak solutions a slight elevation of pressure can be maintained and hemorrhage

simultaneously checked. This can also be accomplished by intramuscular injections.

4. Adrenalin is not indicated in all intestinal hemorrhages. The condition of the blood pressure is the criterion for its use. In hemorrhages of short duration, when the pressure has not fallen to any extent, a judicious dose of nitrites proves of more benefit than adrenalin. When the bleeding has been profuse, however, and a low pressure already exists, it becomes vital that hemorrhage should be checked without further reduction of pressure. Adrenalin finds its use in this field.

5. The use of adrenalin should always be closely followed by blood-pressure observations. A dose sure to be below the safety limit should first be tried and the pressure carefully estimated. If no rise occurs gradually increasing doses may be injected until a slight elevation of pressure is present, in which case we may be certain that enough has been introduced to affect hemorrhage, and at least no significant preliminary increase has resulted.