THE EFFECT OF SYMPATHOMIMETIC AGENTS ON THE CHICK EMBRYO

ROBERT R. GATLING, M.D.

From the Departments of Pathology, St. Dominic-Jackson Memorial Hospital and The University of Mississippi School of Medicine, Jackson, Miss.

Reaction to stress may be manifested by local or general responsiveness. Epinephrine and norepinephrine are two indigenous hormones intimately associated with the stress reaction in both man and experimental animals. Under certain circumstances an altered local reactivity to these substances has been shown to occur. Thomas [1] demonstrated that when endotoxin was administered directly into the circulation, epinephrine became a potent necrotizing agent if injected intradermally. Altered local reactivity to epinephrine also has been shown to occur when this substance is injected into the skin of hypersensitive rabbits following a challenge intravenous injection of specific antigen.[2] Evers and Brunson [3] demonstrated a local necrotizing reaction to epinephrine injected intradermally following stress produced by rotation in a Noble-Collip drum. These 3 independent investigations illustrate a stress reaction produced by (a) a toxic product of bacteria, (b) an immunologic reaction, and (c) purely physical forces. All of these causative factors have one common denominator: the production of dermal necrosis following intradermal injection of epinephrine or norepinephrine.

Although much effort has been exerted in investigation of the pharmacologic actions of epinephrine and norepinephrine, their exact mode of action remains unclear. Extracts from adrenergic nerves have yielded detectable quantities of both substances.[4a] Goldenberg, Pines, Baldwin, Greene and Roh [5] reported that the general effects of norepinephrine on the circulation of the adult seem to be determined by its vasoconstrictor effect and not by any direct stimulant action on the heart. They also stated that epinephrine stimulates the heart and causes vasodilatation. On the contrary, the fetal circulation of the rabbit and guinea pig is reported to be relatively insensitive to both epinephrine and norepinephrine.[6] Epinephrine is known to be a powerful constrictor of the skin and splanchnic vessels, with the exception of those in the liver. Grant and Pearson [7] demonstrated a transient vasodilatation of the vessels of the calf muscles following intravenous infusion of epinephrine, and Allen, Barcroft and Edholm [8] demonstrated that vasodilatation was due to the direct effect of the drug on the vessels. Von Euler stated that the lack

Supported by United States Public Health Service Grant No. A-4510.
Accepted for publication, August 4, 1961.

of knowledge of the mechanism underlying the basic actions of noradrenalin and adrenalin rendered a discussion of the finer points of the differences of the action not fruitful.[4b]

The chick embryo has been used in the investigation of infectious agents, the pathogenesis of diseases, and in the study of some aspects of immunology. The present group of experiments utilized this laboratory model in the investigation of sympathomimetic agents through the production of a seemingly specific lesion. The purpose of this paper is to report the results of these investigations.

Material and Methods

Embryos

Embryonated eggs were obtained from a local hatchery. The eggs had been incubated from 6 to 12 days when obtained and were incubated at 37° C. in a humidified incubator after being received. Except as otherwise stated, eggs incubated 10, 11, or 12 days were used.

The eggs were candled. A 1.5 by 1.5 cm. window was cut through the shell and the chorio-allantoic membrane dropped on the day of the experiment or on the preceding day. The windows were covered by a previously flamed cover glass and sealed by vaspar (vaseline and paraffin mixture) according to the method described by Buddingh.[9] The material to be tested was dropped directly upon the chorio-allantoic membrane, after which the cover glass was immediately replaced. Controls were treated similarly with physiologic saline. A sterile tuberculin syringe fitted with a sterile 24-gauge needle was used to measure the test substance and to drop it upon the membrane. The eggs were harvested by enlarging the window and lifting the embryo.

Sympathomimetic Substances and Other Agents Applied to the Membrane

Ephedrine sulfate (1 ml. ampules containing 0.05 gm.) and epinephrine chloride (1 ml. ampules of 1:1,000 solution) were prepared by Parke-Davis Company. Norepinephrine bitartrate (Levophed®) (4 ml. ampules as a 1:1,000 solution) and Neo-Synephrine® hydrochloride (5 ml. vial as a 1 per cent solution) were prepared by Winthrop Laboratories, New York City. Histamine phosphate (20 ml. vial as a 1:1,000 solution) was prepared by Abbott Laboratories, North Chicago, Illinois. Cortisone acetate (Cortone® acetate) (10 ml. vial containing 50 mg. per ml.) was prepared by Merck, Sharp and Dohme, Philadelphia. Serotonin creatinine sulfate was supplied through the courtesy of Dr. George H. Berryman and Abbott Laboratories. The endotoxin was prepared by Difco Laboratories, Detroit, as *Escherichia coli* lipopolysaccharide 055:B5. Physiologic saline in 30 ml. vials was prepared by Pharmaseal Laboratories, Glendale, California. Largon® (propiomazine hydrochloride) was prepared by Wyeth Laboratories, Inc., Philadelphia.

Except as otherwise stated, epinephrine, norepinephrine, ephedrine and histamine were dropped upon the chorio-allantois undiluted. Neo-Synephrine and Largon were diluted 1:4 with physiologic saline. The endotoxin was suspended in physiologic saline.

Except as otherwise indicated, the individual dosage of norepinephrine and epinephrine was 50 μgm. and of Neo-Synephrine, 125 μgm.

Results

Production and Evolution of the Lesions Produced in the Chick Embryo by Epinephrine, Norepinephrine or Neo-Synephrine

When any of these 3 sympathomimetic agents was dropped upon the chorio-allantoic membrane of the 10 to 14-day chick embryo, a large

cephalic hematoma, apparently subdural in location or extending subdurally, developed. This occurred about the epiphysis and lay just cephalad to the optic lobes (Fig. 1). Occasionally, the lesion extended to the overlying epidermis and spilled out upon the skin surface spontaneously or with the slightest trauma. It also extended about the diencephalon in the subdural space (Fig. 2). In some instances hemorrhage occurred within the ventricles, arising either from the choroid plexus or by extension from the hemorrhage within the subdural space. Occasionally, hemorrhage into and around the gasserian ganglion also was observed (Fig. 3). All embryos that died within a few hours following application of an appropriate sympathomimetic agent displayed this lesion, and it appeared that the hematoma *per se* was sufficient to cause death. In some instances the cephalic hematoma was fully developed as early as 15 minutes following application of the drug. It appeared almost immediately following application of the sympathomimetic agent to the membrane, the short lag period apparently representing the interval of drug absorption. No anatomic alteration of the vessel walls at the site of the lesions was observed. When cephalic hematoma formation was not present or was insufficient to bring about death, hemorrhage into the skin, feather follicles, subcutaneous mesenchyma, and extremities developed, but these lesions began later and progressed in severity for several hours instead of evolving almost instantaneously as did the cephalic hematomas. When marked hemorrhage occurred into the extremities, it was diffuse and distended the tissues just as in hemorrhagic infarction. Welch and Mall[10] carried out a series of experiments using the small intestine of the dog and demonstrated that hemorrhagic infarction occurred under circumstances of reduced arterial blood flow to the point of cessation of pulsations but not to the point of complete blockage. This could be brought about by incomplete occlusion of the supplying artery or by complete occlusion of this vessel in the presence of functioning collateral circulation. The mechanism of hemorrhagic infarction described by Welch and Mall may represent a similar circumstance to that existing in the extremity of the chick embryo.

Since the effects of epinephrine, norepinephrine and Neo-Synephrine were so nearly similar, epinephrine was used to study in detail the mechanism of the lesion.

Modifying Factors

Age. Groups of embryos that had been incubated 7, 8, 10, 11, 13, or 15 days were used. The results are listed in Table I. The lesions are illustrated in Fig. 4.

The conclusions reached from these experiments were that the younger and older embryos were less susceptible to epinephrine than the 10, 11 or

12-day embryos. The mechanism of tolerance in the 7 and 8-day embryos has been pondered. There is some reason to suggest the possibility that the circulating blood volume might be insufficient for hematoma production. There is also the possibility that the vessels were not sufficiently developed by this age to be responsive, either because of immaturity of the smooth muscle or inadequate nerve supply. The latter will be discussed later. The lesions that evolved in the younger embryos developed more slowly than those in the older ones. It seems that when the embryo reaches the age of 15 days it becomes relatively tolerant to sympathomimetic agents.

Temperature. In order to study the effect of body temperature on the development of the lesion, 21 eleven-day embryos were divided into 3 groups. Eight were placed at room temperature (24° C.) for 3 hours

TABLE I

EFFECT OF EMBRYO AGE ON RESPONSE TO 50 μGM. OF EPINEPRINE

No. of embryos	Age (days)	Time interval (between epinephrine application and harvesting)	Cephalic hematoma	Hemorrhage of skin and extremity
17	7	15 min.	None	None
18	8	3 to 16 hr.	Slight	Marked (not all)
41	10, 11 or 12	1 to 16 hr.	Marked	Marked *
17	15	1 to 7 hr.	Minimal	Mild (not all) †

* If cephalic hematoma was marked, the embryo died before skin and extremity hemorrhage could develop.

† One hundred μgm. of epinephrine were used in some of these, but results were similar.

prior to treatment with epinephrine; 8 were incubated at 43° C. for 3 hours prior to treatment, and the remaining 5 were incubated at the usual temperature of 37° C. prior to treatment. The pulsations of the umbilical artery were enumerated under these different circumstances of temperature (Table II). It appeared that the responsiveness to epinephrine was in direct proportion to the body temperature within certain limits (Fig. 5). Three possibilities present themselves to account for the reduced reactivity at low body temperature: (a) diminished absorption due to slowing of the circulation within the membrane; (b) decreased rate of distribution due to reduced heart rate; and (c) diminished responsiveness at the target site, either of biochemical or physical nature. By the same token, the increased responsivness under conditions of elevated temperature may indicate an increase in one or all of these factors.

Dosage. Four groups of 12-day embryos were used. The chorioallantoic membranes were inoculated with 20, 50, 100 or 200 μgm. of epinephrine each. Those receiving as little as 20 μgm. developed as large a cephalic hematoma and as much skin hemorrhage as those receiving

200 μgm. Lesions developing following 100 and 200 μgm. were similar to those produced by 50 μgm. The larger veins in those receiving the larger quantities of epinephrine (100 to 200 μgm.) appeared dilated and quite congested, and some hemorrhage into the muscles was apparent. Because the heart appeared somewhat dilated, it was possible that congestive heart failure may have accounted for the large vessel engorgement.

TABLE II

THE EFFECT OF VARYING THE TEMPERATURE OF THE EMBRYONATED EGGS TREATED WITH EPINEPHRINE (50 μGM.)

No. of embryos *	Incubation temperature	Heart rate (per minute)†	Cephalic hematoma	Hemorrhage of skin and extremity
8	24° C.	68–88	Absent	Rare
5	37° C.	160	Marked	Marked ‡
8	43° C.	176–200	Marked	Marked ‡

* Embryos harvested 90 minutes following epinephrine application.

† Heart rate determined by counting pulsations of umbilical artery.

‡ If cephalic hematoma was severe, the embryo died before developing skin and extremity hemorrhage.

TABLE III

COMPARISON OF EFFECTS OF OTHER SYMPATHOMIMETIC AGENTS

Sympathomimetic agent	Amount (μgm.)	Cephalic hematoma	Hemorrhage of skin and extremity
Epinephrine	50	Present	Present *
Norepinephrine	50	Present	Present *
Neo-Synephrine	125	Present	Present *
Ephedrine	2500	None	None
Serotonin	50	None	None

* When cephalic hematoma formation was marked, the embryos usually died before developing significant skin and extremity hemorrhage.

Effect of Other Sympathomimetic Agents and Histamine

Sympathomimetic agents were dropped upon the chorio-allantoic membrane of different groups of 11-day embryos in quantities indicated in Table III. The embryos in those eggs to which norepinephrine and Neo-Synephrine were applied developed lesions that were indistinguishable from those caused by epinephrine. No lesions similar to those produced by epinephrine or other alterations were visible externally or on cross section in those embryos exposed to serotonin or ephedrine. The effect of histamine was determined by dropping 50 μgm. of this substance upon the membrane. Except for a small focus of hemorrhage in the head of one and slight hemorrhage in one lower extremity of another embryo, no lesions resulted, and the embryos appeared healthy when harvested.

Influence of Cortisone on the Lesion

Effect of Cortisone Alone. Eleven-day embryos were used in all of these experiments. Five mg. of cortisone acetate was applied to the chorio-allantoic membrane in each of 15 embryos. Nine were harvested after 6 hours, and the remaining 6 were harvested after 20 hours. All embryos were alive and appeared healthy. The skin was pink, and no evidence of blanching or hemorrhage was visible.

Effect of Pre-treatment with Cortisone on the Responsiveness to Epinephrine. Fifty-two 11-day embryos were used. Five mg. of cortisone acetate was applied to the chorio-allantoic membrane of each. Fifty μgm. of epinephrine was dropped upon the membrane of each at different intervals of time following the cortisone, as indicated below. Thirteen of the 18 embryos with epinephrine applied 3 hours after cortisone developed cephalic hematomas, and 4 of the remaining 5 had hemorrhage about the optic lobes. A peculiar blanching of the skin was a striking feature in all. Six of the 19 embryos treated with epinephrine 6 hours following cortisone developed cephalic hematomas, and all 19 demonstrated striking blanching of the skin. None of the 30 to which epinephrine was applied to the chorio-allantois 17 or 20 hours following cortisone showed any evidence of cephalic hematoma or skin hemorrhage, but all skin surfaces appeared blanched and bloodless. All embryos were alive when harvested (Fig. 6).

The observations in this group of experiments suggest that cortisone *per se* exerts no detectable effect upon the embryo, but when it is combined with epinephrine, the two are capable of causing widespread vasospasm. If sufficient time elapsed between cortisone application and exposure of the embryo to epinephrine, it was capable of prolonging life and inhibiting the cephalic hemorrhage caused by the latter drug. The ability of cortisone to inhibit hemorrhage appeared to bear a linear relationship to the time interval between its application and that of epinephrine. This seems to indicate that the important determining factor was the amount of cortisone absorbed. If it were due to a direct chemical reaction between cortisone and epinephrine, the time interval would not be important since these substances invariably mix while lying upon the chorio-allantoic membrane.

Effect of Pre-treatment with Cortisone on the Responsiveness to Norepinephrine and Neo-Synephrine. This experiment was carried out in a manner similar to the above except that norepinephrine was used in place of epinephrine and applied 20 hours following pre-treatment with cortisone. No cephalic hematoma occurred, but hemorrhage into the tips of the extremities developed in some. There was no blanching of the skin

as noted in the epinephrine-cortisone experiments described above. The skin of most embryos appeared even more pink than in the normal untreated state (Fig. 6).

The effect of pre-treatment with cortisone on the response to Neo-Synephrine was investigated in a similar manner. Cortisone completely inhibited cephalic hematoma formation in every embryo, but skin and extremity hemorrhage was not inhibited. No blanching of the skin occurred. In this respect Neo-Synephrine seemed to act in a manner indistinguishable from norepinephrine (Fig. 6).

Influence of Endotoxin

Forty-three 11-day embryos were used. Five, 10 or 20 μgm. of endotoxin was applied to the chorio-allantoic membrane of each embryo in 3 groups respectively. After 2 to 4 hours' incubation at 37° C., 50 μgm. of epinephrine was dropped on the chorio-allantois. The reaction to epinephrine was the same as that occurring in the control embryos receiving only epinephrine and no endotoxin. Some embryos receiving endotoxin seemed to exhibit slightly larger cephalic hematomas and more marked skin hemorrhage than the control group, and the vessels of the chorio-allantois appeared atonic and dilated. There appeared a possibility that the effect of endotoxin on vessels might result from its direct action upon smooth muscle. A control group of 16 embryos, to which only endotoxin in quantities varying between 5 and 50 μgm. was applied to the membrane, appeared healthy 10 hours later, but the skin appeared moderately hyperemic. No skin hemorrhages were noted. When the chorio-allantoic membrane was viewed through the dissecting microscope, refractile crystals were visible upon its surface in many instances 3 hours or more after endotoxin application. This suggested the possibility of incomplete or inconstant absorption of this substance. Smith and Thomas [11] described skin hemorrhage in the embryo following application of endotoxin to the chorio-allantoic membrane, but they harvested the embryos after a longer interval of time.

Prevention of the Lesion by Propiomazine Hydrochloride (Largon)

This drug was dropped upon the membranes of some embryos and injected into a chorio-allantoic vein of others. The subjects were divided into 3 groups; after 30 minutes, epinephrine, norepinephrine and Neo-Synephrine were applied to the membranes of each group respectively. The results are listed in Table IV. The effects of these sympathomimetic agents were completely inhibited. No deaths attributable to epinephrine occurred.

Largon was noted to exhibit a direct effect on the vessels of the chorio-

allantois by inducing segmental constriction of the arteries and arterioles and ectasia of the veins, with marked sludging and stasis of the blood.

Discussion

It would seem that the significance of these investigations is principally that of offering another experimental model through which one might contemplate the mode of action of certain of the sympathomimetic

Table IV

THE EFFECT OF PRE-TREATMENT WITH LARGON (PROPIOMAZINE HYDROCHLORIDE)

No. of embryos	Age	Amt. of Largon (mg.)	Mode of administration	Harvested after	Lesions
9	12 days	0.25	Intravenous	2–6 hr.	None
9	12 days	0.5	Topical to membrane	2–6 hr.	None
10	11 days	0.5	Topical to membrane	20 hr.	None

agents. The investigation of the lesions provides 3 facets of information: (a) the drugs that produce hemorrhagic lesions in the chick embryo; (b) the responsiveness to these drugs following pre-treatment with cortisone; and (c) the drugs which produce no lesion in the embryo at all. The rapid evolution of the lesion and the apparent absence of anatomic alteration in the vessel walls seem to indicate that these drugs in some way affect the tone of vessels, seemingly the veins and capillaries. The investigations of Welch and Mall [10] showed that hemorrhagic infarction occurred principally because of diminished but not complete cessation of blood flow to the part. They demonstrated that this phenomenon was not the result of damage to the vessel wall or to venous obstruction primarily but in effect was the result of marked reduction of arterial blood flow. They also pointed out the necessity of pulsations to prevent sludging at the site of bifurcation of capillaries. In view of these observations, one might postulate that cephalic hemorrhage and hemorrhage into the extremities in the chick embryo produced by sympathomimetic agents is due to their action as vasopressors to the point of cessation of vascular pulsation but not cessation of flow. On the other hand, there is no absolute proof that these substances act as vasopressors in the chick embryo. When epinephrine has been injected into the wattles, comb or skin of the full-grown chicken, we have not observed blanching. This, however, does not completely exclude the possible vasopressor action in the 8 to 13-day chick embryos.

In connection with this, pre-treatment of the embryos with cortisone seemed to bring about a striking alteration in the action of sympathomimetic agents (epinephrine, norepinephrine and Neo-Synephrine). Cortisone not only appeared capable of completely preventing the cephalic hemorrhage induced by these drugs, but embryos treated with epineph-

rine following pre-treatment with cortisone responded by profound blanching of the skin. Norepinephrine and Neo-Synephrine differed from epinephrine in that no skin blanching occurred following pre-treatment with cortisone, and hemorrhage into the extremities was not prevented. Pre-treatment with cortisone seemed to divide the 3 drugs into 2 groups. In the chick embryo, cortisone possesses the faculty of rendering to epinephrine a profound vasopressor action; suppression of the cephalic hemorrhage may be due directly to that function. The skin blanching following pre-treatment with cortisone is evidence of vasoconstriction caused by epinephrine under these circumstances. The observation that cortisone will not completely inhibit cephalic hematoma formation when epinephrine is applied to the chorio-allantois within 6 hours following cortisone treatment indicates that the interaction of these two substances is due neither to direct chemical reaction nor to local action at the site of application. It is more likely that the activity of each is peripheral and is mediated through the nerve supply to the arteries, arterioles and capillaries. Cortisone has long been regarded as an anti-inflammatory agent, and its mode of action under these circumstances may be correlated in some way with epinephrine or norepinephrine. The interaction of epinephrine and cortisone might explain the vascular collapse and shock associated with acute adrenal insufficiency and its successful prevention and treatment by cortisone.

The chick embryo affords a rather unique laboratory model for an evaluation of the role of the nerve supply to vessels in the pharmacologic action of these sympathomimetic agents, cortisone and a phenothiazine derivative. The extra-embryonic membranes, including the chorio-allantois, are devoid of nerve supply. The peripheral nervous system of the embryo, on the other hand, is well along in development by the eighth day of incubation, and it is apparent that there are both innervated and noninnervated blood vessels connected with the same circulatory system. It appears significant that those without nerve supply (chorio-allantoic vessels) have remained unaffected by the action of both sympathomimetic agents and of cortisone even though they have been exposed to the full impact of these agents by direct application. This seems to exclude any direct action by these agents on the vascular smooth muscle of the chick embryo as a basis for pharmacologic action, and suggests that their mode of action is mediated in some way through the nerve endings or nerve supply to the vessels. In connection with the latter, it would be of interest to know if the local reaction to epinephrine in the hypersensitive rabbit, in the rabbit pre-treated with endotoxin and in the rabbit rotated in the Noble-Collip drum might be prevented by denervation of the blood vessels.

Of all drugs tested, only one, propiomazine hydrochloride, was shown

to have a direct effect on the smooth muscle of blood vessels, independently of nerve supply. This drug was observed to cause segmental constriction of arteries and ectasia of veins and capillaries in the chorio-allantois. The vessels of the chorio-allantois are noninnervated, and the action of propiomazine hydrochloride on them indicated that its effect was directly upon smooth muscle. Since this substance prevented the hemorrhagic lesions induced by certain sympathomimetic agents, it was presumed to have done so by rendering smooth muscle nonreceptive to stimuli mediated through the nerve endings.

Summary

The chick embryo provides an experimental model for demonstrating an anatomic lesion induced by certain sympathomimetic agents. Epinephrine, norepinephrine and Neo-Synephrine, when dropped upon the chorio-allantois, initiated cephalic hematoma formation or skin and extremity hemorrhage in 10, 11, and 12-day chick embryos. Ephedrine and serotonin produced no lesions. Pre-treatment of the embryos with cortisone inhibited cephalic hematoma formation. Following pre-treatment with cortisone, epinephrine initiated a striking blanching of embryonic skin; norepinephrine and Neo-Synephrine did not. The reactivity of the embryo with or without cortisone pre-treatment indicated a division of these sympathomimetic drugs into 3 groups and thereby offered a means of classifying them according to their pharmacologic actions. The possible pathogenesis of the lesions is discussed. The action of sympathomimetic agents was completely prevented by propiomazine hydrochloride. Evidence is offered to show that the action of epinephrine, Neo-Synephrine and norepinephrine on blood vessels is mediated through the nerve supply; this seems also to be true of cortisone.

References

1. Thomas, L. The role of epinephrine in the reactions produced by the endotoxins of gram-negative bacteria. 1. Hemorrhagic necrosis produced by epinephrine in the skin of endotoxin-treated rabbits. *J. Exper. Med.*, 1956, **104**, 865–880.
2. Gatling, R. R. Altered reactivity to epinephrine in the hypersensitive rabbit. *J. Exper. Med.*, 1958, **108**, 441–452.
3. Evers, C. G., and Brunson, J. G. Studies on experimental shock: production of ischemic necrosis of the skin by an intradermal injection of endotoxin or vasopressor amine. *Am. J. Path.*, 1960, **37**, 551–567.
4. Von Euler, U. S. Noradrenaline; Chemistry, Physiology, Pharmacology and Clinical Aspects. Charles C Thomas, Springfield, Ill., 1956, (a) pp. 133 ff.; (b) p. 198.
5. Goldenberg, M.; Pines, K. L.; Baldwin, E. deF.; Greene, D. G., and Roh, C. E. The hemodynamic response of man to nor-epinephrine and epinephrine and its relation to the problem of hypertension. *Am. J. Med.*, 1948, **5**, 792–806.

6. DORNHORST, A. C., and YOUNG, I. M. The action of adrenaline and noradrenaline on the placental and foetal circulations in the rabbit and guinea-pig. *J. Physiol.*, 1952, **118**, 282–288.
7. GRANT, R. T., and PEARSON, R. S. B. The blood circulation in human limb; observations on the differences between the proximal and distal parts and remarks on the regulation of body temperature. *Clin. Sc.*, 1938, **3**, 119–139.
8. ALLEN, W. J.; BARCROFT, H., and EDHOLM, O. G. On the action of adrenaline on the blood vessels in human skeletal muscle. *J. Physiol.*, 1946, **105**, 255–267.
9. BUDDINGH, G. J. In: Viral and Rickettsial Diseases of Man. RIVERS, T. M. (ed.). J. B. Lippincott Co., Philadelphia, 1952, ed. 2, pp. 112–113.
10. WELCH, W. H., and MALL, F. P. Experimental Study of Haemorrhagic Infarction of the Small Intestine in the Dog. In: Papers and Addresses by William Henry Welch. The Johns Hopkins Press, Baltimore, 1920, Vol. 1, pp. 77–109.
11. SMITH, R. T., and THOMAS, L. The lethal effect of endotoxins on the chick embryo. *J. Exper. Med.*, 1956, **104**, 217–231.

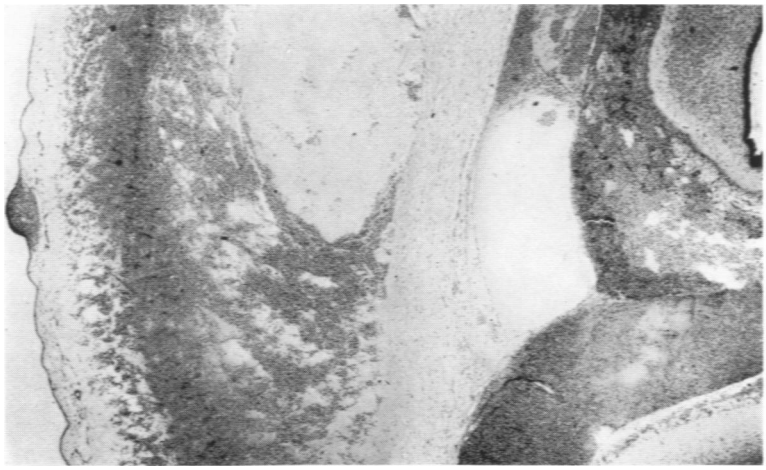
[*Illustrations follow*]

Legends for Figures

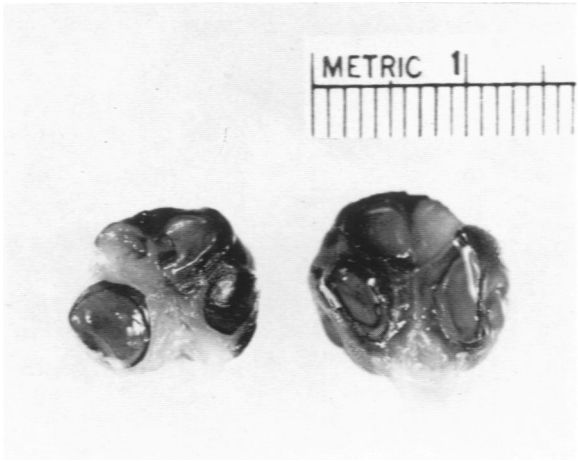
Fig. 1. Cross section through a cephalic hematoma. Epidermis of the scalp, containing a feather follicle, covers the surface on the left; a subcutaneous hematoma lies immediately below. Extensive subdural hematoma is identifiable beneath the developing membranous bone of the skull. Hematoxylin and eosin stain. × 40.

Fig. 2. Cross section of the head through a hematoma. The posterior portion of the eyes are the paired pigmented defects beneath the brain. The subdural hematoma lies in the groove between the hemispheres and extends around one hemisphere within the subdural space. × 2.

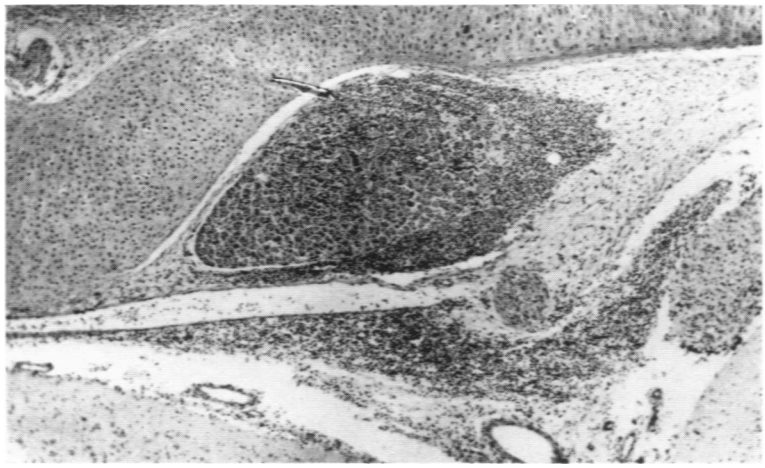
Fig. 3. Hemorrhage into and around the gasserian ganglion. Hemorrhage below the ganglion is within the subdural space. Hematoxylin and eosin stain. × 70.



1



2



3

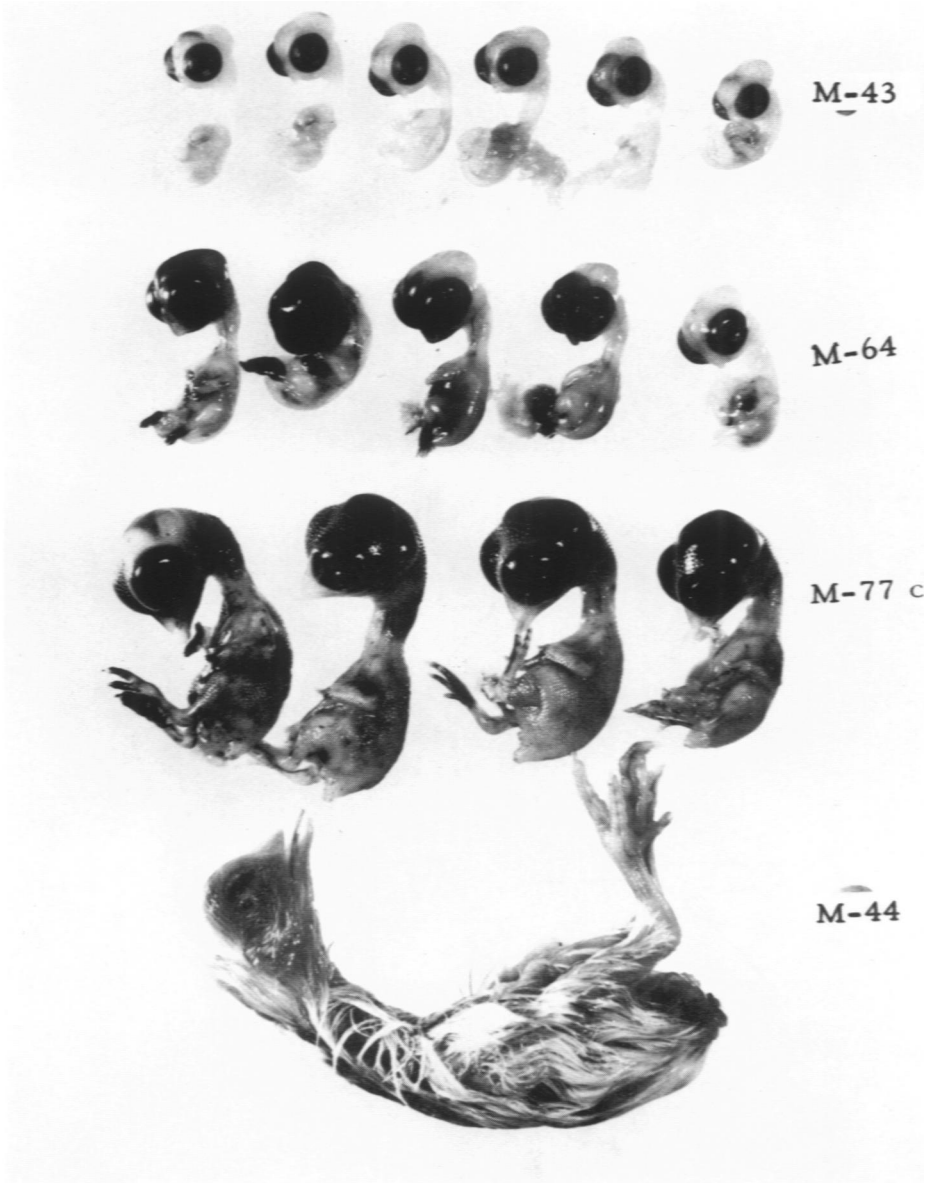
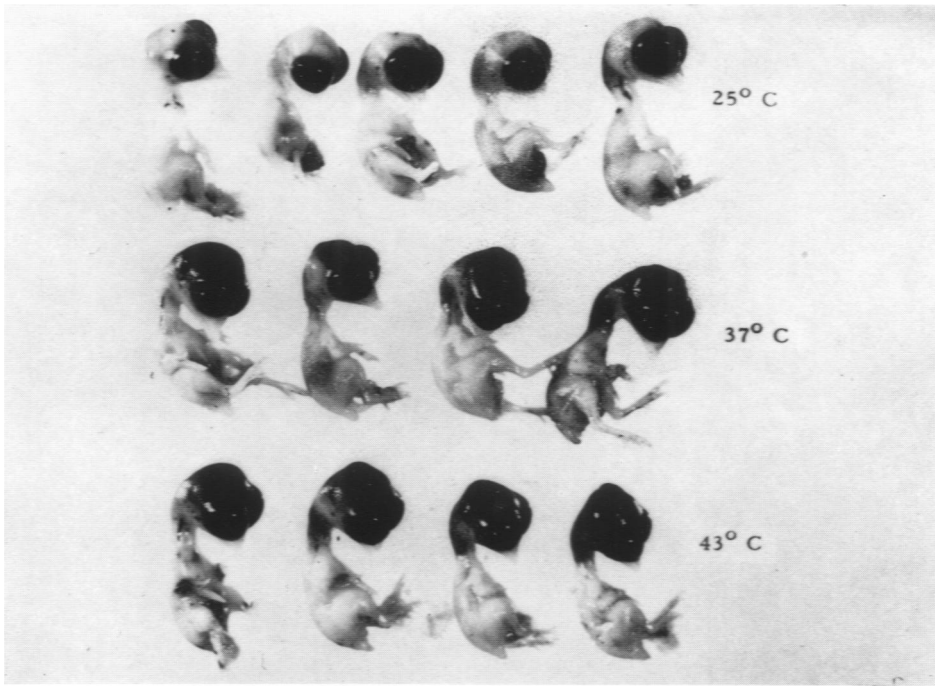
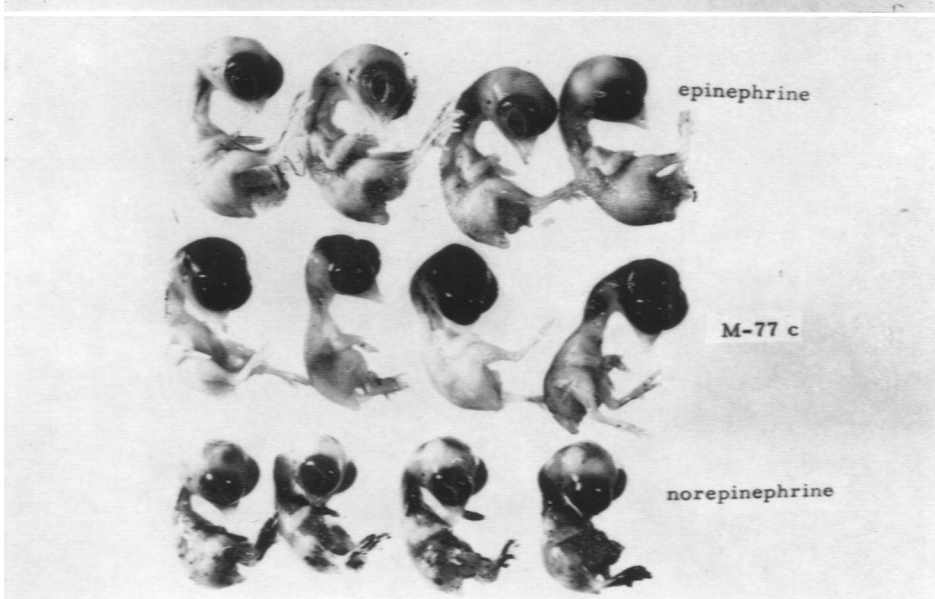


FIG. 4. Embryos of different ages and their responses to 50 μgm. of epinephrine dropped upon the chorio-allantoic membrane. M-43, 7 days; M-64. 8 days; M-77c. 11 days; M-44. 15 days. M-64 and M-77c illustrate both hemorrhage in the extremities and cephalic hematoma formation. × 1.



5



6

FIG. 5. The effect of body temperature on the reactivity to epinephrine in the 11-day embryo. The temperatures listed are those at which the embryos were kept for 3 hours preceding and following application of 50 μgm. of epinephrine to the chorio-allantois. × 0.7.

FIG. 6. The effect of pre-treatment with cortisone on the reactivity of the 11-day embryo to epinephrine and norepinephrine. M-77c is the epinephrine control group not pre-treated with cortisone. Prevention of cephalic hematoma is evident. The lack of hemorrhage in the skin and extremities of the epinephrine-treated group and the fairly extensive hemorrhage in extremities and skin in the norepinephrine-treated embryos are apparent. × 0.7.