

Furthermore, it can be seen from the table that there is a relationship between the concentration of the venom solution and the rapidity with which petechiae first appear. The latent period increases with the decrease of venom concentration. Once the hemorrhage is initiated, however, there is no striking difference to be observed as far as the degree and the number of hemorrhagic manifestations are concerned. Higher dilutions of the moccasin venom which just fail to produce hemorrhages in the chicken embryo sometimes caused bradycardia and death.

Summary. The addition of moccasin venom in sufficient concentration to 3-day-old chicken embryos produces hemorrhages in the vascular network. This method may be used for the demonstration of hemorrhagins in venoms. Further studies should be made to determine whether this method is applicable for the quantitative determination of hemorrhagins.

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Influence of Drugs on Chicken Embryo and on Its Reaction to Sera Containing Forssman Antibodies.

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The addition of sera containing Forssman antibodies to 3-day-old chicken embryos which are taken out of the eggshell and kept in beakers, causes the following phenomenon: The vascular network contracts, the embryo turns around, sinks into the yolk and finally dies (Baumann and Witebsky¹). This phenomenon is to be interpreted as the sequela of a reaction between the Forssman antigen of the chicken embryo and the corresponding antibodies of the added serum. It can be produced only by sera containing Forssman antibodies (normal "rabbit type" sera and Forssman antiserum). Thus, we are dealing with a phenomenon which parallels the so-called inverted anaphylactic shock of guinea pigs following the injection of Forssman antiserum.

The nature of the mechanism of anaphylactic phenomena is still a moot question. Some authors claim that they are due to physico-chemical changes of the cells following antigen-antibody reaction;

¹ Baumann, A., and Witebsky, E., *Compt. rend Soc. Biol.*, 1934, **116**, 10; *Annales de l'Inst. Pasteur*, 1934, **53**, 282.

others believe that chemical substances formed by antigen-antibody reaction are the effective factor. The work of Dale, Kendall, Lewis, Manwaring and their coworkers has shown that histamine can produce reactions similar to or even identical with anaphylactic phenomena.² Since the addition of normal "rabbit-type" sera and Forssman antisera to the chicken embryo produces an anaphylactic reaction, it seemed of interest to determine whether histamine can produce a similar phenomenon in this preparation. However, various amounts of histamine (Imido-Roche) in the concentration of 1 mg. to 0.005 mg. dropped on the chicken embryo did not produce the phenomenon.* Thus, while there is a remarkable parallelism between the inverted anaphylactic shock of the guinea pig and the vascular phenomenon of the chicken embryo, there exists this marked difference in the susceptibility of this preparation to histamine.

Other drugs have been examined with respect to their ability to produce the vascular phenomenon in the chicken embryo (acetylcholine, atropine, epinephrine, ergotamine, strophanthin, digitalis, insulin, ether, chloroform). Although certain pharmacological effects were observed, none of the examined drugs caused the typical phenomenon.

The pharmacological effect of certain drugs toward the chicken embryo, however, is of interest since the 3-day-old embryo consists almost exclusively of vascular system in this stage of development. The first group of drugs tested comprised atropine, epinephrine, ergotamine and acetylcholine. These are known to affect the autonomic nervous system. They proved ineffective against the chicken embryo. Drugs of the digitalis group (digitalin, strophanthine) caused a typical bradycardia, irregularity and stoppage of the heart beat.† As a third group, anesthetics were tried. The addition of a few drops of ether did not show any influence, while chloroform caused cardiac standstill in a few minutes.

There was next studied the influence of the drugs upon the production of the vascular phenomenon in the chicken embryo by means of "rabbit type" sera. None of the following drugs showed any inhibitory influence upon the production of the vascular phe-

² For literature and discussion see Dale, H., *Lancet*, 1929, **216**, 1285; Feldberg and Schiff, "Histamin," Berlin, Springer, 1930.

* The application of Witte-Peptide (1% solution in physiological saline) also failed to produce the vascular phenomenon in the chicken embryo.

† The toxic effect of strophanthin (ouabain in physiological saline) in a dosage of $\frac{1}{2}$ mg. is not inhibited by previous or simultaneous addition of atropine sulphate. (0.5 mg.)

nomena—atropine, acetylcholine, ergotamine, epinephrine and histamine. Since the inhibitory influence of anesthetics on anaphylactic reactions is well known the study of their effect on the chicken embryo phenomenon was of interest. Ether in sublethal amounts does not impede the phenomenon. A few drops of 5% aqueous emulsion of chloroform produces a temporary cardiac standstill. Smaller amounts are ineffective and larger amounts cause death of the embryo. When an effective serum is added to a chicken embryo in which temporary cardiac standstill is induced by the addition of the proper amount (as determined by previous trial) of chloroform, the typical vascular phenomenon appears even though slightly retarded. This experiment shows that the added serum is absorbed, regardless of the arrest of circulation due to the cardiac standstill.‡ Too large an amount of chloroform, however, produces a permanent cardiac standstill. Such embryos do not react any longer to the addition of an effective serum.

A second form of temporary cardiac standstill, that caused by lower temperature, should be reported in this connection. If chicken embryos are placed in the icebox at a temperature of 4-6°C. a cardiac standstill results after a few minutes. When returned to the incubator the heart again starts beating. While the cardiac standstill due to chloroform does not prevent the phenomenon from occurring after the addition of effective sera, no reaction appears if the serum is added to an embryo whose heart beat is stopped under the influence of the cold. The phenomenon occurs, however, if the embryo is put back into the incubator. Apparently, therefore, either the serum is not absorbed in the cold or the suppression of the phenomenon is due to the fact that complement, which is necessary for the production of the vascular phenomenon of the chicken embryo, does not act at a lower temperature.

Summary. 1. In spite of the fact that histamine is able to cause reactions similar to anaphylactic phenomena in other animals, it does not produce in the chicken embryo the vascular phenomenon which follows the addition of Forssman antibody containing serum. 2. Drugs, such as acetylcholine, atropine, epinephrine, ergotamine, likewise fail to produce any reaction similar to the vascular phenomenon. 3. Drugs of the digitalis group induce bradycardia, irregularity and eventually produce cardiac standstill. 4. Chloroform

‡ The vascular phenomenon can also be produced in so-called monsters, *i. e.*, embryos with malformations consisting more or less of the vascular network only. Although there is no manifest circulation, the vessels of such monsters contract in the same way as in normal embryos. This observation was made 6 times.

stops the heart beat. With low concentrations of chloroform, a temporary cardiac standstill is produced. 5. Chicken embryos, treated with chloroform in a dosage which causes a temporary cardiac standstill react as normal embryos to the addition of effective serum, *i. e.*, they show typical vascular phenomenon. 6. The phenomenon cannot be produced in embryos whose heart beat is stopped by exposure to ice box temperature.

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**Pulmonary Blood Velocity in Congestive Heart Failure.
Velocity in Pulmonary Venous Circuit.**

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Our observations demonstrate that there are changes chiefly, and sometimes solely, in the velocity of the pulmonary venous circulation clearly related to congestive heart failure. This velocity was estimated by utilizing 2 methods for studying pulmonary blood flow (1) the ether time¹ which serves as a measure of the rate of blood flow in the pulmonary arterial system and (2) the taste or saccharine time² which serves as a measure of the rate of blood flow through the combined arterial and venous circuit, the so-called "crude pulmonary circulation". By subtracting (1) from (2) we obtained readings of velocity in the pulmonary venous system. The normal average ether time is 5 to 9 seconds, the taste or saccharine time is 14 to 16 seconds, and the average velocity in the venous circuit is 6 to 9 seconds, practically identical with that in the arterial circuit.

Figures within normal limits were observed in 100 hospital individuals from various diseases, the greatest number of whom were free of cardiac disease and the rest recovered from congestive heart failure. On the other hand, in 30 hospital individuals with cardiac disease and in various stages of congestive failure lasting over many months, there were always prolonged saccharine time readings but the ether figures were within normal limits; the arithmetical

¹ Hitzig, W. M., *PROC. SOC. EXP. BIOL. AND MED.*, 1934, **31**, 935; Miller, H. R., *Ibid.*, 1934, **31**, 842.

² Fishberg, A. M., Hitzig, W. M., King, F. H., *PROC. SOC. EXP. BIOL. AND MED.*, 1933, **30**, 651