4169

Cause of Death Following Intravenous Injection of Ox and Dog Serum into Rabbits.

JACOB RABINOVITCH. (Introduced by Leo Loeb.)

From the Department of Pathology, Washington University School of Medicine, St. Louis, Mo.

Marked divergencies occur[1, 2, 3, 4, 5, 6, 7, 8] concerning the mode of action of foreign sera in causing death after intravenous injection. We repeated and extended in various directions the investigations of Loeb and his collaborators, and of Kusama. Our results are as follows:

I. *Injection of ox serum.* When we injected a lethal dose of ox serum into the ear vein of a rabbit, we found in the lungs removed immediately after the death of the animal, very extensive occlusion of the capillaries as well as of the larger vessels by thrombi. In the capillaries these thrombi appear to consist of agglutinated red blood cells only; whereas in the larger vessels there was also an admixture of white blood cells and possibly of platelets; no fibrin could be made out anywhere. All the other organs examined microscopically showed merely congestion. The injection of a sub-lethal dose of ox serum caused only partial occlusion of the pulmonary vessels by such thrombi and the animal therefore survived. When heparin was injected in quantities sufficient to prevent coagulation of the blood together with a lethal dose of ox serum, it did not prolong the life or prevent the death of the animal. Also the microscopic picture of the various organs, remained the same as after injection of the ox serum alone.

II. *Injection of dog serum.* After injection of a lethal dose of dog serum, microscopic examination of the lungs also showed massive occlusion of the capillaries and larger vessels by thrombi. In the capillaries the thrombi appeared to consist of massed-together, pale red blood cells, without any fibrin being visible; in the larger vessels however, fibrin could be definitely seen in the

[1] Landois, *Die Transfusion des Blutes.* Leipzig, 1875.
[2] Flexner, Simon. *J. Med. Res.*, 1902, viii, 316.
[3] Loeb, Leo, Strickler, A. and Tuttle, L. *Virchow's Archives*, 201, 5, 1910.
[4] Kusama, S. *Ziegler's Beitr.*, 1913, v, 55.
[5] Airila, Y. *Skand. Arch. fur Physiol.*, 1914, xxxi, 388.
[6] Coca, A. *J. Immun.*, 1919, iv, 219.
[7] Drinker, C. K., and Bronfenbrenner, J., *J. Immun.*, 1924, ix, 5.
[8] Friedberger, E., and Seidenberg, S., *Z. f. Immun. Forsch.*, 1927, li, 216.

thrombi. The finding of fibrin in the larger vessels as well as the action of heparin in combination with dog serum, to be referred to shortly, suggests very strongly however, that the thrombi formed in the capillaries also contained fibrin, which was however, too fine to be recognized microscopically. When heparin was injected in combination with a lethal dose of dog serum, the life of the animal was prolonged for a long time and in some cases death was prevented altogether. Microscopically no thrombi were seen in the lungs of the animals that thus survived. Experiments *in vitro* showed that heparin in addition to its anticoagulative action is capable of preventing hemolysis of the rabbit's red blood cells normally caused by dog serum. Thus heparin prevents the formation of fibrin thrombi in this case in a double way namely, (1) by preventing coagulation and (2) by diminishing the setting free of the tissue coagulin (thrombokinase) from the erythrocytes.

Following the injection of a lethal dose of either ox or dog serum there resulted a very marked reduction of all the cellular elements of the rabbit's blood. In sublethal doses, we found that ox serum produced only a temporary reduction of the cellular elements of the blood which in the course of 24 hours tended to return to normal. Dog serum, on the other hand, produced a noticeable reduction in the number of red blood cells only, and this reduction was still present after 24 hours because of the hemolysis caused by injection of dog serum. Heparin which did not influence the effect of ox serum on rabbit's blood cells, prevented the reduction of the blood cells caused by dog serum, owing to its antihemolytic effect. After injection of ox serum the loosely agglutinated cells which are held back in various organs are freed in the course of 24 hours and are again free to circulate in the vessels.

It follows from our experiments that both ox and dog serum when injected in lethal doses intravenously into rabbits cause the death of these animals through the formation of thrombi which in the case of ox serum consist of agglutinated erythrocytes and in the case of dog serum of fibrin thrombi. While this conclusion seems definite in the case of dog serum, there remained in the case of ox serum still the possibility that constriction of the pulmonary vessels may after all be the real cause of death and that the presence of agglutination thrombi is merely simulated. We attempted therefore, to demonstrate directly the occlusion of the pulmonary vessels by examining on glass slides thin slices of lung removed rapidly before secondary changes could take place, from rabbits following injection of lethal doses of ox serum. By exerting gentle pressure, we could squeeze out from the vessels numerous

thrombi consisting of agglutinated red blood cells which were readily seen under the microscope.

Our results confirm and extend thus the results obtained by Loeb, Strickler and Tuttle and they are contrary to the conclusions of Kusama. There remains of course the possibility that in case of agglutinative sera a constriction of pulmonary vessels may play a certain role in addition to the formation of agglutination thrombi: but at best the significance of the latter factor could only be of a subsidiary character.