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Changes in Tissues After Intravenous Injection of Colloidal Thorium Dioxide.

I. C. WEN AND T. S. JUNG. (Introduced by A. B. D. Fortuyn.)

From the Departments of Anatomy and Radiology, Peiping Union Medical College.

Tissue changes following intravenous injections of thorium preparations have been well described by Kadrnka and Rossier,[1] Irwin,[2] Ravenna,[3] Shute and Davis,[4] and others, but a study of very early reactions seems to have been neglected. In our studies on the effect of colloidal thorium dioxide* upon blood and tissue cells of the rabbit, we have found that the early phase of reactions after a single intravenous injection is of great importance.

We injected 7 rabbits with 1 cc. per kg. and another 7 with a single dosage of 3 cc. per kg. They were killed 10, 15, 30 minutes, 1, 1½, 3, and 6 hours after the injection. Fresh blood smears were examined and various organs were removed and fixed in Zenker-formalin mixture. Histological sections were stained with acid fuchsin and methyl green. The green dye brings out the thorium in such a selective way that its identification inside as well as outside of the cell is greatly facilitated. In comparing the changes in the tissue of rabbits injected with 1 cc. with those of 3 cc., we found that the difference is only a matter of degree. In fact, rabbits treated with a large dosage proved to be more favorable for our purposes than cases injected with a small dosage. The following account is based upon observations in the 3 cc. dosage specimens.

Ten minutes after injection, thorium dioxide is readily identified in the spleen as a homogeneous mass of various sizes, distributed everywhere in the sinuses. Such a mass is not found in any other organ. In the specimen of 15 minutes after injection, it is found that thorium is present predominantly in the venous capillaries of the bone marrow and the liver. Here, the thorium appears to be in a free, finely granular state. The spleen at this time is full of thorium granules in the red pulp. As the latter structure is filled with slowly filtering blood, it is to be expected that more thorium particles are

[1] Kadrnka, S., and Rossier, J., *Acta Radiol.*, 1931, **12**, 369.

[2] Irwin, D. A., *Canad. Med. Assn. J.*, 1932, **27**, 130, 353.

[3] Ravenna, P., *Klin. Wchenschr.*, 1932, **2**, 2151.

[4] Shute, E., and Davis, M. E., *Arch. Path.*, 1933, **15**, 27.

* The thorium used in this work is a commercial preparation known as "thorotrast," obtained from Chemische Fabrik von Heyden, Radebeul-Dresden, Germany

accumulated in the spleen than elsewhere. Due to this manner of accumulation the spleen shows a definite shadow in the roentgen-film. In the 30-minute specimen the spleen contains even more thorium granules than previously, while in the liver, bone marrow, suprarenal glands, lymph nodes, etc., no appreciable change in the amount of the thorium is found. This picture remains unchanged until 1 to 1½ hour after the injection. Then, marked changes take place not only in the blood cells but also in the histiocytic elements. A sudden increase in number of polymorphonuclears is noted in the sinusoidal spaces of the spleen, in the venous capillaries of liver and bone marrow, and also in the general circulation. This condition persists for several days after the injection. Meanwhile numerous mononuclear cells contain thorium granules in the splenic sinuses. Such cells are present both in fresh smear preparations and in fixed sections. Some of them contain only a few granules while others are heavily loaded. Morphologically they resemble in many respects the large lymphocytes, except that they have more cytoplasm and many vacuoles. In the specimen of 3 hours after injection, we find no marked changes of the amount of thorium in the spleen, liver, bone marrow, and other organs. The thorium-masses are now practically in the form of granules. These are found in quite a few Kupffer cells in the liver. When the 6-hour specimen is examined, the thorium-loaded Kupffer cells become increased in number, but the presence of thorium in their cytoplasm does not distort their stellate shape. In spleen, bone marrow and lymph node the thorium granules are found to adhere to the reticular fibers as well as to the cell processes of the reticulo-endothelial meshwork. In the endothelial lining of the common blood vessels we have not found any thorium granule.

From 6 to 24 hours after the injection we have not found any change in the organs mentioned above, except that more reticular and Kupffer cells take up the thorium granules. After 24 hours, again there is no marked alteration in the amount of thorium in the different organs, but the distribution of thorium granules in the cells is of some interest. Some of the Kupffer cells and reticular cells are so heavily loaded with the thorium granules that they become round. Besides them, the hepatic cells everywhere contain very fine thorium granules. It should be pointed out that the mononuclear elements containing thorium granules in the spleen now become decreased in number.

As to the changes for periods longer than 24 hours, we have made observations on rabbits injected with 1 cc. and 3 cc. per kg.

body weight respectively, and killed them 48 hours, 1 week, 1 month, and 5 months after the injection. Our findings do not materially differ from those already reported. It is therefore unnecessary to give an account. However, two points have been insufficiently emphasized by previous reports. (1) A week or so after the injection the thorium-loaded cells always tend to group together in the form of cell-masses. Only a few of them seem to get into the lumen of the venous sinuses and are carried with the blood into the right heart and into the capillaries of the lungs, which they may obstruct. In the lung they also may be eliminated. But most of them persist in the spleen, liver, and bone marrow for a considerable time. In our histological preparations we are unable to find any elimination of such aggregated masses through the kidney. (2) A shifting of the thorium from the spleen to the liver takes place about one to 2 months after injection. In both small and large dosage specimens the thorium present in the spleen becomes decreased about 40 days after injection and meanwhile the amount in the liver is increased.

7115 C

Experimental Bronchomoniliasis in Sensitized Rabbits.

T. J. KUROTCHKIN AND C. E. LIM.

From the Department of Bacteriology and Immunology, Peiping Union Medical College.

We reported[1] on the production of experimental bronchomoniliasis in rabbits following intratracheal administration of living cultures of pathogenic *Monilia tropicalis*. It was shown that the development of the disease was dependent upon pre-existing damage brought about by repeated intravenous injections of small doses of chaulmoogra oil. We also succeeded in producing regular sensitization of guinea pigs with cultures of various *Moniliae*. This led us to assume that perhaps sensitization of rabbits with monilia cultures may also result in an increased susceptibility of these animals to their subsequent inoculation.

The present experiment is an attempt to test this assumption. Five normal rabbits were anesthetized with ether and 0.5 cc. of a thick suspension containing 1/5 of a 2 or 15 day agar culture of *Monilia tropicalis* was injected into the trachea of the animals.

[1] Lim, C. E., and Kurotchkin, T. J., *Nat. Med. J. China*, 1930, **16**, 537.