After 6 to 8 hours these animals were injected intraperitoneally with lethal doses of Pneumococci types I, II, and III. These cultures were grown in Avery's medium and suspended in saline solution to produce a suspension containing approximately 300,000,000 organisms per cc. The amounts given, varying from 0.1 to 0.25 cc., were adjusted so that death of the animals could be controlled and occurred at periods varying from 3 to 24 hours.

The animals in the various series received a respective antigenic injection approximately 6 hours previous to the administration of the infecting dose of the pneumococcus. In one series, 2 antigenic doses were given at 24 hour intervals and an infecting dose 6 hours following the last injection. Control animals for the infecting dose were run with each series and the effects of the antigenic injection were also noted in other control animals.

While in certain instances some of the supposedly protected animals survived for several hours longer than the infection control animal, at other times the control lived somewhat longer than those that had received the antigenic dose or doses.

Our procedure does not conform to that used by Steinberg in that our infecting microorganism was more virulent and that repeated injections to produce a hyperleucocytic immunity were not administered.

The results of our experiments would indicate that in white mice, the injections of various antigenic substances employed as stimulators for a leucocytic increase, failed to show any evidence of protection to this animal against the production of fatal pneumococcal peritonitis.

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Effects of Toxic and Non-toxic Doses of Thorium Dioxide in Various Animals.

C. J. TRIPOLI AND E. V. HAAM.

From the Departments of Pathology of Charity Hospital and Louisiana State University Medical Center.

The value of the method of roentgenographic visualization of the liver and spleen in the human is, in our opinion, dependent only upon the possible dangers involved in the intravenous administration of stabilized colloidal suspensions of thorium dioxide (Thorotrast).

We have undertaken a series of experiments to determine the histopathological changes in the tissues of animals that have been given various intravenous doses of thorium dioxide over varying periods of time.

Seventy-nine animals, comprising 4 dogs, 15 albino rats, 18 guinea pigs, 20 white mice, and 22 rabbits, have been used in this work. All animals were injected with doses varying from that which permits good visualization (0.8 gm. per kg. body weight) to 10 times this dose. An additional number of animals were used as controls in each experiment. The dogs and rabbits were injected intravenously, whereas the guinea pigs, white mice and rats were injected by the intracardiac route. The complete dose was given over a period of 3 days, one-third of the total dose each day. The animals were then killed at intervals of one day, one week, one month and 6 months following the injection of both small and large doses of the thorium preparation.

The following observations were made: All animals which received 0.8 gm. per kg. body weight showed no changes in appetite, skin, body weight, susceptibility to infections or propagation of the species. The animals were all living and well up to the time of being sacrificed.

Several animals receiving 10 times the smaller dose (8.0 gm. per kg. body weight) showed toxic effects. Three guinea pigs and 2 rabbits lost considerable weight and were apparently ill for 2 weeks, but recovered and were killed at the end of one month. Two rabbits, one guinea pig and 3 white mice died within one to 3 days following the last injection. Thus 69 animals survived throughout the time of the experiment without any notable changes.

These surviving animals were sacrificed and autopsied at varying intervals following administration of the drug with the following gross findings: No gross changes nor any evidence of any type of hemorrhage was noted in animals receiving 0.8 gm. per kg. body weight, irrespective of time elapsing between final administration of the drug and death, ranging from one day to 6 months. In those animals receiving 10 times the smaller dose, the liver and spleen were paler than normal. In none was there any hemorrhage present. Two rabbits and one mouse of this series were pregnant. The embryos were living at the time of autopsy. In some of the animals intracardially injected, the mediastinal lymph nodes were markedly enlarged.

Histopathological study revealed the following:

1. Animals which received doses of 0.8 gm. per kilo.

a. Spleen. With such animals sacrificed at the end of 24 hours, a few thorium particles were found free in the finer capillaries. Reticulo-endothelial cells were found already containing the thorium particles. At the end of one week, no free thorium was found, but many reticulo-endothelial cells contained the metal. At the end of one month, fewer reticulo-endothelial cells were found containing the thorium, much reduced in amount. At the end of 6 months, a very few reticulo-endothelial cells scattered throughout the organ contained the thorium particles. No evidences of hemorrhage or fibrosis were noted in any instance.

b. Liver. The liver as regards the free particles of thorium and the reticulo-endothelial cells presented in all cases the same picture as described for the spleen at the end of corresponding time intervals. The liver cells of early sacrificed animals occasionally contained a few particles of thorium, but in animals later sacrificed, thorium was not present.

c. None of the animals receiving the small dose showed any thorium in any organ other than the liver and spleen. No histopathological changes could be demonstrated in any organ of any of the animals as compared to apparent healthy control animals.

2. Animals which received 8 gm. per kilo.

a. Spleen. Many thrombi of thorium particles were present in the capillaries and free particles were found in the splenic pulp at the end of one day. Minute areas showing beginning necrosis were present. At the end of one week, the reticulo-endothelial cells had engulfed all of the thorium and none was found free. No necrosis or fibrosis was present. Guinea pigs and rabbits showed the thorium particles in the center of the Malpighian bodies, whereas the mice and white rats had the thorium in the cells of the periphery of the lobule. At the end of one month, the only change in the picture was the presence of a smaller amount of thorium as estimated by visual means. At the end of 6 months, certainly over one-half of the thorium had disappeared from the reticulo-endothelial cells of the spleen.

b. Liver. The changes were quite similar to those described for the spleen, there being thrombi of thorium particles present in the finer capillaries and marked parenchymatous degeneration of the liver cells, with no actual necrosis noted. At the end of one month a few thrombi remained, but retrograde changes of the liver cells were no longer noted, all the thorium being then found in the reticulo-endothelial cells. Animals sacrificed at the end of 6 months

showed that a great deal of the thorium had disappeared from the cells. No hemorrhage or fibrosis was noted at any time.

c. Kidneys. White mice killed one week after injection showed exudate and thickening of the glomerular capsule with small thrombi in the glomerular loops. Guinea pigs, rabbits and albino rats showed degeneration of the proximal convoluted tubules. Animals sacrificed one month following injection show no renal lesions.

d. Animals showed thorium particles present in the reticulo-endothelial cells of the bone marrow, adrenal glands and lung.

e. Brain, heart, vascular system, pancreas, gastro-intestinal tract, genito-urinary organs, placenta and embryonic tissues showed no evidence of thorium particles except for renal glomerular thrombi as previously noted in animals sacrificed one week after injection. The smaller animals receiving accidental mediastinal dosages while attempting intracardiac injections showed thorium in the pericardium and mediastinal lymph glands.

Summary. 1. The reticulo-endothelial cells, particularly in the liver and spleen, have been shown constantly to exhibit their characteristic property of engulfing foreign particles from the circulation. 2. Non-toxic doses produce no histopathological changes in the tissues examined and the amount of thorium in the reticulo-endothelial cells is diminished after one month and greatly so after 6 months. 3. Toxic doses produce, in some instances, emboli and minute necrosis in the spleen and retrograde changes in liver and kidney which may or may not be permanent.

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A Study of Splenic Contraction in Various Animals.

E. V. HAAM, C. J. TRIPOLI AND E. B. LEHMAN.

From the Departments of Pathology and Radiology, Charity Hospital, and Louisiana State University Medical Center, New Orleans, La.

Since Barcroft's[1] work, a great number of authors have emphasized the importance of the spleen as a reservoir for red blood cells. Numerous experiments have been performed to visualize the dilatation and contraction of the spleen. Barcroft tried to observe the movements of this organ in the dog through a celluloid window

[1] Barcroft, *Erg. Physiol.*, 1926, **26**, 818.