

14503

Recognition of Liver Cirrhosis Induced by Paradimethylaminoazobenzene (Butter Yellow) by X-ray and Thorium Dioxide.

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A method of determining in the living albino rat the presence, the degree and the progression of liver damage induced by feeding butter yellow is presented. Changes of the spleen can also be observed. The advantages of the procedure are as follows: it permits continuation of an experiment until a desired lesion is obtained and it allows regeneration studies by establishing the severity of the lesion in given animals.

The procedure consists in administering intracardially 0.5 cc of thorium dioxide sol (thorotrast). A similar dose is given every 2 to 3 months if the experiment is prolonged over a long period. The thorotrast is deposited principally in the sinusoids of the liver and capillaries of the spleen. A roentgenogram allows the visualization of both of these organs. A satisfactory visualization is obtained by the use of low voltage, high amperage, and a fast exposure of 1/20 of a second. The rats can be put to sleep with ether or sodium pentobarbital if difficulties are experienced with the animal awake.

We observed in the haematoxylin and eosin preparations of cirrhotic liver tissue of rats fed butter yellow that the thorotrast was concentrated in the connective tissue. The thorotrast was intracellular. There was relatively little of the chemical in the sinusoids of areas in which liver cells were preserved. The thorotrast was singularly absent or only in minute quantities in parts of liver showing duct hyperplasia, duct adenocarcinoma, hepatoma, and adenocarcinoma of liver cells.

Correlation of the microscopic preparations and the roentgenograms indicated that the visible radiopaque lines outlined connective tissue which replaced liver cells and distorted the organ architecture. The nonvisualized areas represented the more or less intact liver tissue. Evaluation of the visualized and non-visualized area established the degree of damage and scarring.

Thorium dioxide sol is lodged largely in the capillaries of splenic pulp. There are occasional small accumulations of the chemical in the periphery of the follicles. Visualization of the spleen allows determination of its size. Spreading out of the radiopaque lines may be interpreted to indicate abnormal accumulation of substances in the pulp.

Intravenous administration of thorium dioxide in people to visualize the liver and the spleen was introduced by Radt¹ and Oka.² The method was used extensively for a number of years in the diagnosis of hepatic disorders until questions were raised of the possible injurious action of thorium dioxide. Stewart, Einhorn, and Illick³ demonstrated by shadowgrams the radio-activity of the chemical within the tissues. Orr, Popoff, Rosedale, and Stephenson,⁴ on the basis of their experiments, advised against administering thorium dioxide to human beings because the substance is not eliminated from the body, it blocks the reticuloendothelial system, it is radio-active and severely damages liver tissue. The last assertion is contrary to the findings of other investigators.⁵ Our own experience indicates that the tissue changes are minimal. A more recent report by Yater and Coe⁶ who followed 286 patients over a period of more than 10 years, denies any remote or immediate ill effects and stresses the value of the method in the diagnosis of cirrhosis, new growths, and abscesses of liver.

Haam, Tripoli, and Lehman⁷ employed

¹ Radt, P., *Klin. Wchnschr.*, 1929, **8**, 2128.

² Oka, M., *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1929, **40**, 497.

³ Stewart, W. H., Einhorn, M., and Illick, H. E., *Am. J. Roentgenol. and Rad. Therap.*, 1932, **27**, 53.

⁴ Orr, C. R., Popoff, G. D., Rosedale, R. S., and Stephenson, B. R., *Radiology*, 1938, **30**, 370.

⁵ Tripoli, C. J., *Am. J. Clin. Path.*, 1934, **4**, 212.

⁶ Yater, W. M., and Coe, F. O., *Ann. Int. Med.*, 1943, **18**, 350.

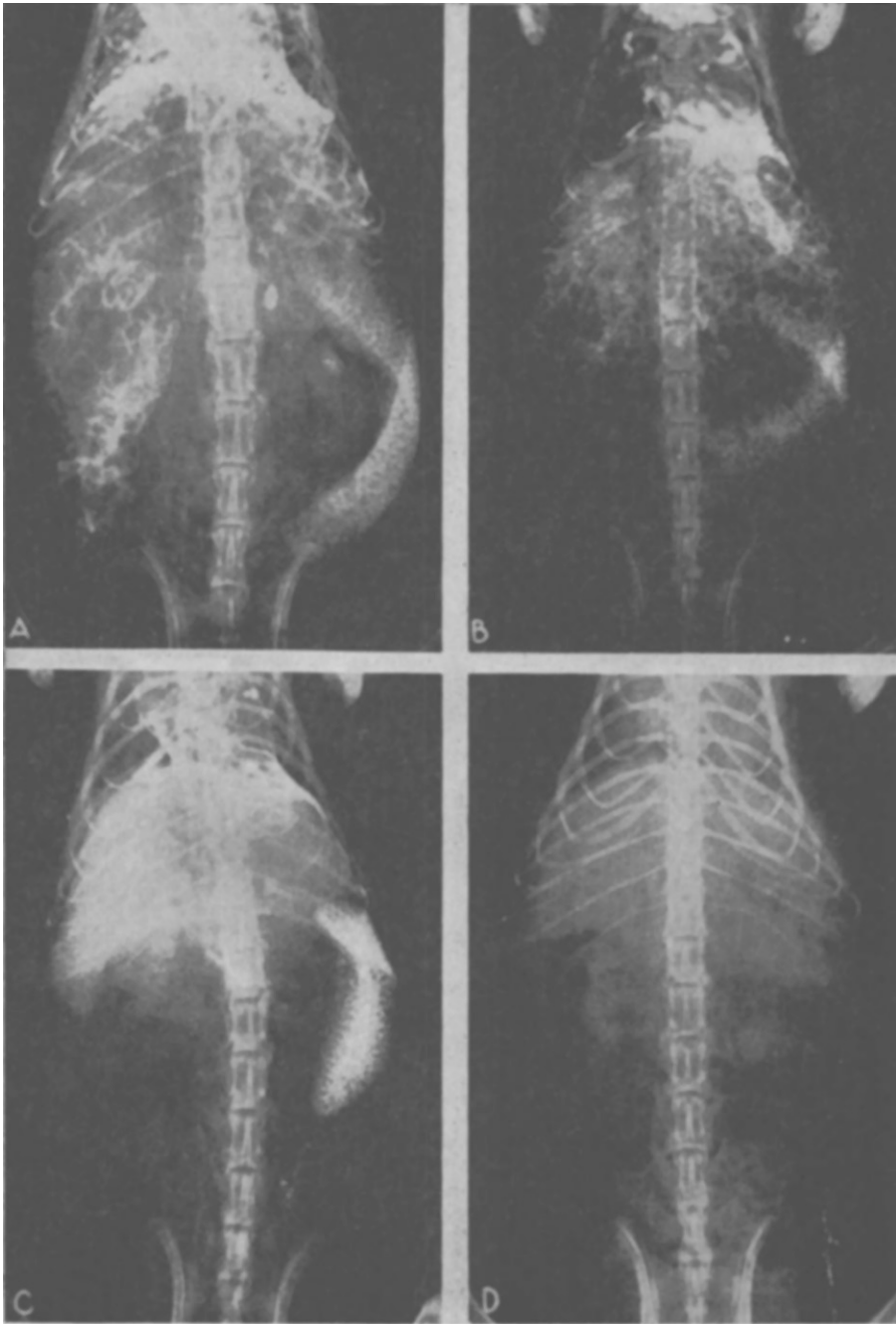


FIG. 1.

Roentgenograms of albino rats which were fed butter yellow and some of which were injected intracardially with thorium dioxide (thorotrast). A and B represent rats with different degrees of liver cirrhosis and splenic enlargement following a diet of ground brown rice, carrots, and butter yellow for approximately two months. Note the irregular outlines of liver tissue. The visualized lines correspond to connective tissue. Compare with C which is a visualization of a normal liver and spleen. D. Roentgenogram of an albino rat without thorium dioxide. The animal had liver cirrhosis corresponding in severity to that of B. Note absence of signs of liver disease.

thorium dioxide in studying contractions of the spleen in various animals. Tripoli⁵ obtained visualization of liver and spleen in dogs, rats, guinea pigs, mice, and rabbits, and Shute and Davis⁸ in rabbits and dogs. The latter investigators state that thorium dioxide prac-

tically disappears from the liver and spleen in 2 or 3 months and the cells regain almost a normal appearance.

Summary. A method of following the course of liver cirrhosis and splenic enlargement induced by feeding butter yellow to albino rats is described. The procedure consists of intracardiac injection of 0.5 cc of thorium dioxide sol (thorotrast) followed by roentgenograms of the liver and spleen.

⁷ Haam, V. E., Tripoli, C. J., and Lehman, E. B., *Proc. Soc. Exp. Biol. and Med.*, 1932, **29**, 1056.

⁸ Shute, E., and Davis, M. E., *Arch. Path.*, 1933, **15**, 27.

14504

Potent Typing Sera Produced by Treatment of Donors with Isolated Blood Group Specific Substances.

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A rise in titer of isoagglutinins has been observed in patients following the erroneous transfusion of incompatible blood. There has been no uniform confirmation of this observation as in some instances the antibody titer did not change. Aubert, Boorman, and Dodd¹ reported an increase in isoagglutinin titer of A patients following the injection of several hundred cc of B plasma and of B patients treated with A plasma.[†] It would seem to be of interest to find out whether the purified group specific substances also will produce a rise in isoantibody titer when injected into human beings.

The blood group specific substances^{2,3,4,5}

used in the investigations to be reported were prepared by the Eli Lilly Company. The material consisted of a mixture of AB substance (isolated from the horse stomach) and A substance (isolated from the hog stomach.) Three to 5 mg AB substance and 5 to 10 mg A substance were dissolved in 10 cc of normal saline solution and dispensed in vials after being tested for sterility and potency.

The determination of the titer of the test sera was done in the following way: decreasing amounts of the donor's serum in volume of 0.2 cc were mixed with 0.2 cc of 1 to 2% suspension of washed, freshly-obtained blood cells belonging to different groups. After standing for 15 minutes, the tubes were centrifuged at medium speed for one minute. Reading of the degree of agglutination was done macroscopically after the tubes had been shaken slightly.

In the first series of experiments 3 donors belonging to groups O, A, and B received 10

* Observations made before entrance into active military service while fellow in Clinical Pathology, Buffalo General Hospital, Buffalo, New York.

¹ Aubert, E. F., Boorman, K. E., and Dodd, B. E., *J. Path. and Bact.*, 1942, **54**, 89.

[†] According to personal communication Wiener obtained increases in isoagglutinin titers in at least half of his donors following injection of pooled plasma.

² Witebsky, E., and Klendshoj, N. C., *J. Exp. Med.*, 1940, **72**, 663.

³ Witebsky, E., Klendshoj, N. C., and Swanson, P., *J. A. M. A.*, 1942, **116**, 2654.

⁴ Witebsky, E., Klendshoj, N. C., and Swanson,

P., *Neutralization of Isoagglutinins Anti-A and Anti-B in O Blood by Means of the Addition of the Isolated Blood Group Specific Substances, Blood Substitutes and Blood Transfusion*, Charles C. Thomas, 1942, 327.

⁵ Klendshoj, N. C., McNeil, Crichton, Swanson, P., and Witebsky, E., *Arch. Int. Med.*, 1942, **70**, 1.