A METHOD OF PRODUCTION OF CIRRHOSIS OF THE LIVER WITH SPLENOMEGALY AND ASCITES IN RABBITS BY MEANS OF CARBON TETRACHLORIDE

L.S. Rubetskoi and R.N. Korotkina

Division of Pathomorphology (Head – Dr. Med. Sci. D. S. Sarkisov) and the Biochemical Laboratory (Head – Dr. Biol. Sci. A. S. Konikova) of the A. V. Vishnevskii Institute of Surgery (Dir. – Active Member AMN SSSR A. A.Vishnevskii) of the AMN SSSR, Moscow
(Presented by Active Member AMN SSSR A. A. Vishnevskii)
Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 50, No. 7. pp. 122-124, July, 1960
Original article submitted October 26, 1959

Carbon tetrachloride is often used to produce lesions of the liver tissue in animals [1, 2, 4]. Animals differ in their sensitivity to this compound. Rabbits, for example, possess high sensitivity to carbon tetrachloride, and this can be a serious obstacle to the production in these animals of frank cirrhosis of the liver: The animals often die before sclerosis of the organ develops. It is therefore important to develop methods of rendering rabbits susceptible to the action of carbon tetrachloride which will lead to the gradual development of significant cirrhotic changes in the liver tissue, reaching the stage of appearance of ascites and splenomegaly.

The technique which we recommend consists of the administration of carbon tetrachloride to rabbits in the form of separate courses, in the intervals between which the animals remain untreated in any way. Carbon tetrachloride is given to the rabbits twice a week, subcutaneously, in a dose of 0.2 ml (a 40% solution in peach oil) per kg body weight. After the first 12-14 injections an interval of 40-50 days is given, and this is followed by a second course of 8-10 injections, and then another interval, slightly longer than the first, and so on. The alternation of courses of injections of carbon tetrachloride with periods when no injections are given is controlled throughout the entire experiment by the protein fractions of the blood serum, for according to data in the literature and to previous research by one of us [3], an increase in the γ-globulins and a decrease in the serum albumins are associated with anatomical changes in the liver tissue in the process of development of cirrhosis. We investigated the serum protein fractions by the paper electrophoresis method, on the average, once every 10 days. The results showing the course of the changes in the serum protein fractions in the rabbits throughout the experiment are given in Fig. 1.

It may be seen from the curves that, after the first course of injections (1-1.5 months), a significant increase takes place (from 40 to 80%) in the serum γ-globulins, and an appreciable decrease (from 7 to 30%), in the albumin content. In the interval between the first and second courses of administration of carbon tetrachloride, a decrease in the γ-globulins and a slight increase in the albumins are observed, but in one rabbit, in which the least deviation from normal followed as a result of the first course of injections, a return to the original values was observed.

The second course of injections of CCl_4 is accompanied by a second sharp increase in the γ-globulins and a fall in the albumins; when this period again is followed by an interval, however, a clear tendency is once more found towards normalization of the serum protein fractions. A third course of carbon tetrachloride

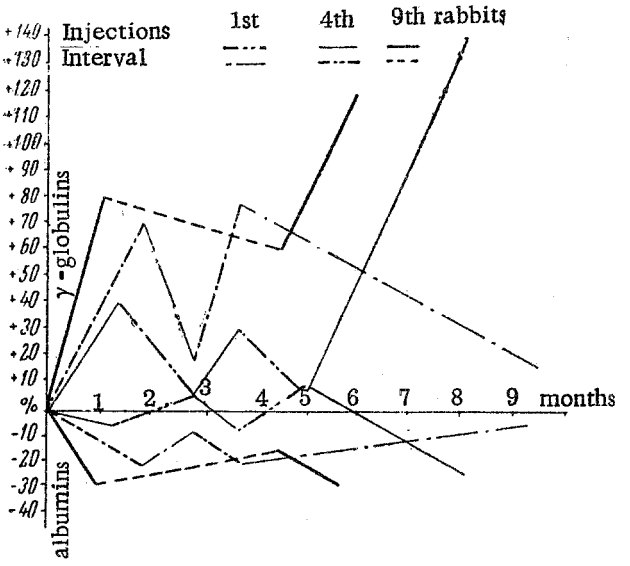

Fig. 1. Course of the changes in the serum protein fractions in rabbits during periods of administration of carbon tetrachloride and in the intervals between injections.

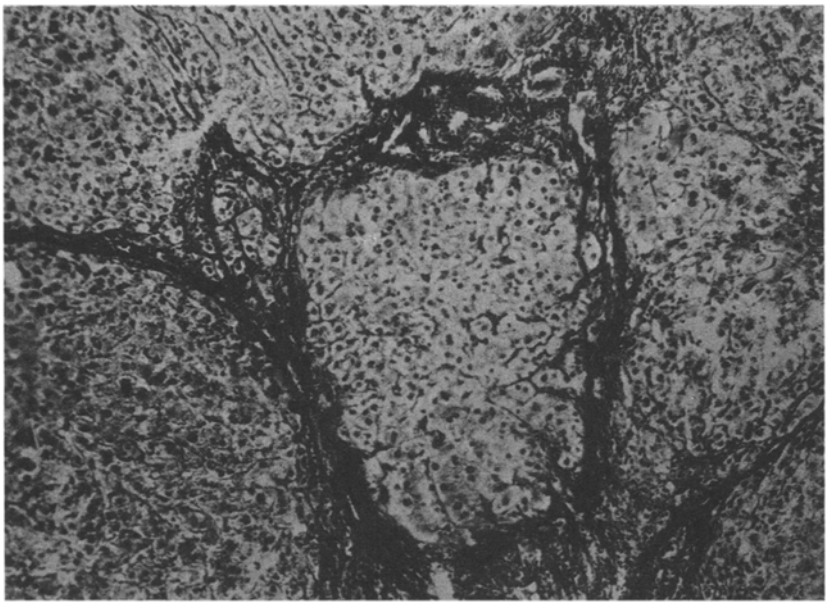

Fig. 2. Liver biopsy of a rabbit 8 months after the beginning of the experiment (3 courses of injections and 2 intervals). Well-marked annular cirrhosis of the liver.

injections, given to one of the experimental animals, gave the sharpest increase in the γ-globulins and the most significant fall in the albumins.

The administration of carbon tetrachloride thus causes considerable changes in the protein composition of the blood serum; when the action of the pathogenic factor is discontinued, however, these changes are partially reversed. The reparative processes in the periods between injections prevent the early death of the animals, as is observed after the continuous administration of carbon tetrachloride, and it enables the development of a more slowly progressive cirrhosis. It must be mentioned that the longer the duration of the experiment, the shorter must be the injection periods and the longer the intervals between them.

As a control of the morphological changes we performed laparotomy on animals after every 2-3 months, examined the liver and removed a piece of tissue for histological investigation. Frank cirrhosis, accompanied in certain cases by considerable enlargement of the spleen and ascites, could be observed in all animals without exception after 6-8 months of the experiment. On histological examination of the liver, an abundant proliferation of connective tissue composed of coarse fibers and a great decrease in hepatic tissue were observed (Fig. 2). Against this background, on the surface of the organ appeared multiple nodules, 0.4-0.5 cm in diameter. These nodules, being regenerative formations, gradually increased in size during the experiment.

It should be emphasized that when the experiment was performed in this way, in spite of the well-marked changes in the liver tissue, the animals remained for a long time in a completely satisfactory condition. This method may thus be used for the trial of various therapeutic measures in cirrhosis of the liver at various stages.

SUMMARY

To prevent an early death of animals with artificially induced cirrhosis of the liver it is suggested that carbon tetrachloride should be administered not continuously, as is usually done, but in separate courses, interrupted by periods free of injections. The protein fractions of the blood are periodically determined and biopsy is performed to control the condition of the liver. Cirrhosis of the liver, in a number of cases accompanied by ascitis and splenomegaly, develops in all the animals in 7 to 8 months.

LITERATURE CITED

1. S.M. Leites and T.S. Yakusheva, Arkh. Patol. No. 4, 44 (1949).
2. P.Ya. Mytnik, Fiziol. Zhur. 26, 296 (1939).
3. O.P. Samarina and L.S. Rubetskoi, Voprosy Med. Khimii 5, 54 (1959).
4. G.R. Cameron and W.A.E. Karunaratne, Path. and Bact. 42, 1(1936).