

PARADOXICAL EFFECT OF CARBON TETRACHLORIDE WHEN ADMINISTERED AT DIFFERENT FREQUENCIES

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As a result of the less frequent administration of a nonlethal dose of carbon tetrachloride (0.2 ml of a 40% solution of CCl_4 once every 2 weeks) to mice, more of the animals die and they do so sooner than if more frequent injections are given of the same dose (on alternate days). This paradoxical effect can be tentatively explained by the much greater intensification of the speed of reparative regeneration of the liver tissue in response to the more frequent action of the toxic agent.

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One of the manifestations of the toxic action of carbon tetrachloride on the body is diffuse vacuolar and fatty degeneration of the liver tissue. After a single injection of carbon tetrachloride the structure of the liver tissue is restored on the average after 12 days [4]. This takes place through a regeneration reaction consisting of cell proliferation coupled with restoration of the normal structure of the degeneratively changed hepatocytes (intracellular regeneration). The outcome of the poisoning is determined by the relationship between the degenerative and reparative processes. In this connection it was decided to examine the character of the degenerative and regenerative processes in the liver tissue during administration of carbon tetrachloride at different frequencies, i.e., when the relationship between these processes differed. Despite the numerous studies which have been undertaken of the action of carbon tetrachloride in liver tissue, no investigations have hitherto been carried out for this purpose.

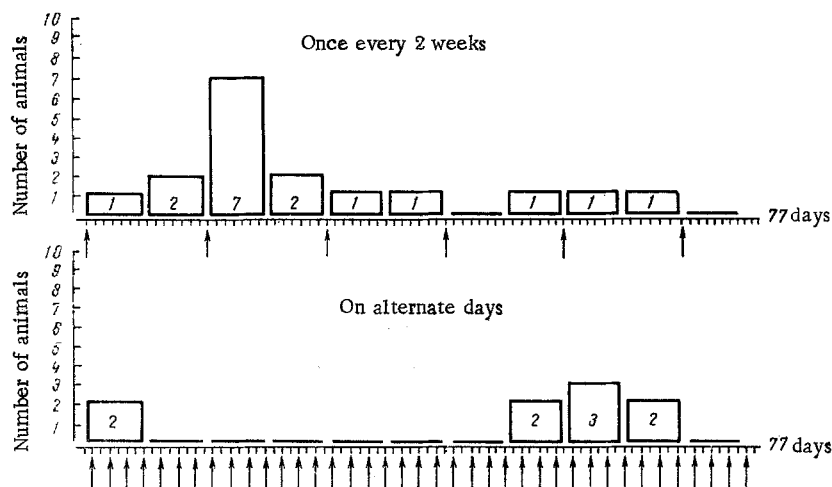


Fig. 1. Graph showing death of mice after receiving CCl_4 injections at different frequencies. Top graph: CCl_4 injected once every 2 weeks; bottom graph: CCl_4 injected on alternate days. \uparrow denotes successive injections of CCl_4 .

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EXPERIMENTAL METHOD

Experiments were carried out on albino mice weighing 18-20 g, divided into three groups: the animals of group 1 received CCl_4 every other day, those of group 2 received CCl_4 once every 2 weeks, and group 3 was the control. The dose of CCl_4 given each time to all the animals was 0.2 ml of a 40% solution in peach oil. Once injection of this dose of CCl_4 caused the death of 4-5 mice from 100 tested in the course of the first 2-6 days. The experiment was repeated three times, using 60 mice with 20 in each group on each occasion. The total number of mice was therefore 180.

EXPERIMENTAL RESULTS

The general result of this investigation was that after the less frequent administration of carbon tetrachloride (once every 2 weeks), most of the animals died, and they did so much sooner than mice receiving the same dose more frequently (on alternate days).

It is clear from Fig. 1, which shows the dynamics of death of the mice in one of three stereotyped series of experiments, that if CCl_4 was injected once every 2 weeks most (12) of the animals died during the first month of the experiment. A further 5 animals died during the next 6 weeks. Hence, in the course of 10 weeks, 17 of the 20 mice of this series of experiments died. The character of the mortality was different among animals receiving CCl_4 on alternate days. It also follows from Fig. 1 that the total number of mice dying in the first 10 weeks in this group (9) was much lower than in group 1 (17). Moreover, the overwhelming majority of animals of this group (7 of 9) died in the 8th-10th week of the experiment.

Hence, among animals receiving 6 injections each of CCl_4 (1.2 ml of a 40% solution) in the course of 11 weeks, death occurred much more often and sooner after the beginning of the experiment than among mice which received 38 injections each in the course of the same period (total 7.6 ml of a 40% solution).

Histological examination of the dying mice of both groups revealed stereotyped changes: marked cloudy swelling and vacuolar and fatty degeneration of the liver, amounting in some cases to zones of necrosis of the liver tissue, together with considerable infiltration of the liver by lymphocytes, plasma cells, and polymorphonuclear leukocytes. The results can be tentatively explained as follows. Previous investigations carried out in the same laboratory [1] have shown that with an increase in the number of injections of carbon tetrachloride, animals develop a state of increased tolerance to this compound. This follows, in particular, from the fact that the most marked degenerative changes in the liver cells usually develop in animals after the first injections of CCl_4 and not at the end of the experiment. Other evidence is given by the fact that areas of necrosis of liver cells were observed only after the first or second injection, if given at an interval of 2-3 days, and were not found in the later stages of the experiment, even after frequent injections of this poison. Death of the animals occurred after the first injections of CCl_4 also, and thereafter was much less frequent. In the later periods the stage of increased tolerance was replaced by a stage of decompensation and by death of the animals [3].

The mechanisms of the increased resistance of the body as a whole and of particular organs to the action of CCl_4 have not yet been explained. Even at this stage, however, the structural basis of these mechanisms can be conjectured.

As a result of the first injection of CCl_4 degenerative changes arise in the liver tissue. Parallel with them, reparative regeneration develops. If the interval between successive injections is short, the intensity of the reparative reaction in the liver tissue increases much more than if longer intervals separate the injections. This has been demonstrated previously by autoradiographic investigation of the regenerating liver in animals exposed to pathogenic agents at different frequencies.

It has been shown, in particular, that after more frequent injections of carbon tetrachloride the number of labeled hepatocytes, i.e., of cells intensively synthesizing DNA, was many times greater than their number in the liver of mice receiving fewer injections of this compound [2]. It has also been shown that with an increase in the number of CCl_4 injections hypertrophy of the liver cells takes place, associated with enlargement of their nuclei and hyperplasia of their ultrastructures [1].

There are thus two ways in which the cells may have its resistance to a pathogenic factor increased: 1) intensification of the rhythm of regeneration; 2) hyperplasia of the tissue structures (cells and intracellular organoids).

The results of these experiments suggest that the much greater toxic action of CCl_4 when administered infrequently can be explained by assuming that under these conditions it induces less intensive regeneration processes than when injected more frequently.

LITERATURE CITED

1. K. I. Dzarakhokhov, Relationship between Destructive and Regenerative Processes in the Liver and the Frequency of Action of a Pathogenic Stimulus, Author's Abstract of Candidate Dissertation, Moscow (1969).
2. L. D. Krymskii, B. V. Vtyurin, K. V. Botsmanov, et al., Byull. Éksperim. Biol. i Med., No. 9, 105 (1968).
3. D. S. Sarkisov and L. S. Rubetskoi, Ways of Recovery of the Cirrhotic Liver [in Russian], Moscow (1965).
4. G. Cameron and W. Karunaratne, J. Path. Bact., 17, 1 (1936).