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# Carbon Tetrachloride Injury of the Liver. The Protective Action of Certain Compounds.*

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In a previous communication[1] results of experiments in dogs were reported showing that sodium thioglycollate conferred the same order of protection of the liver against acute chloroform injury as did protein and methionine. These studies were interpreted as showing the importance of the –SH group in the protective mechanisms of the hepatic cell against one form of acute injury. The criterion for hepatic damage was the bromsulphalein excretion—a physiologic test. Histologic study of the livers was not carried out because of the nature of the experiments.

This report is concerned with a study of the protective action of certain –SH and other compounds against acute hepatic injury produced by carbon tetrachloride in the rat. In this study histologic criteria were employed. The types of injury produced by carbon tetrachloride and chloroform respectively are not necessarily closely related phenomena.

Injection of .1 cc of carbon tetrachloride subcutaneously into rats weighing 150 g results in 24 hours in characteristic hepatic lesions.[2] There are many foci of enlarged hepatic cells with clear vacuolated cytoplasm; the nuclei are slightly reduced in size. In the central portions of such foci, hepatic cells are shrunken, and their cytoplasm is dense and eosinophilic. Associated with these lesions there is a varying degree of round cell infiltration. Most of the foci appear about the central lobular vein; some are in the periphery of the lobules. These lesions are ephemeral since 2 weeks after a single injection they are no longer present and the liver appears normal.

The vacuolation of the hepatic cells is not closely associated with the accumulation of fat in the liver since staining with Sudan III reveals no fat in the enlarged cells. The latter are the result of acute edema.

Fifteen rats received injections of .1 cc of carbon tetrachloride subcutaneously and a maximal extent of the lesions described above was observed in histologic sections of the liver taken at necropsy 24 hours later. In 2 animals the lesions were of limited size. These findings indicate that in exceptional instances there is an unusual degree of resistance to the noxious effects of carbon tetrachloride.

A series of observations were then carried out in which various agents were injected intraperitoneally immediately following the subcutaneous injection of carbon tetrachloride. The animals were killed 24 hours later and the livers removed for histologic study. Failure of development of the lesions or an appreciable reduction in their number and size was interpreted to indicate that the agent injected intraperitoneally conferred a degree of protection against the acute injury by carbon tetrachloride (Fig. 1).

The results are summarized in Table I. Since the occasional animal appears to be resistant to the effects of carbon tetrachloride a definite protective action was ascribed to an injected agent only if at least approximately 40% of the animals tested showed lesions of limited extent or no appreciable lesions. The table reveals that a very marked protection was afforded by sodium thioglycollate; considerable protection was also obtained with sodium glycollate. Glutathione afforded appreciable protection. Sodium thiomalate, sodium malate, and cystein afforded definite protection but less marked than the previously

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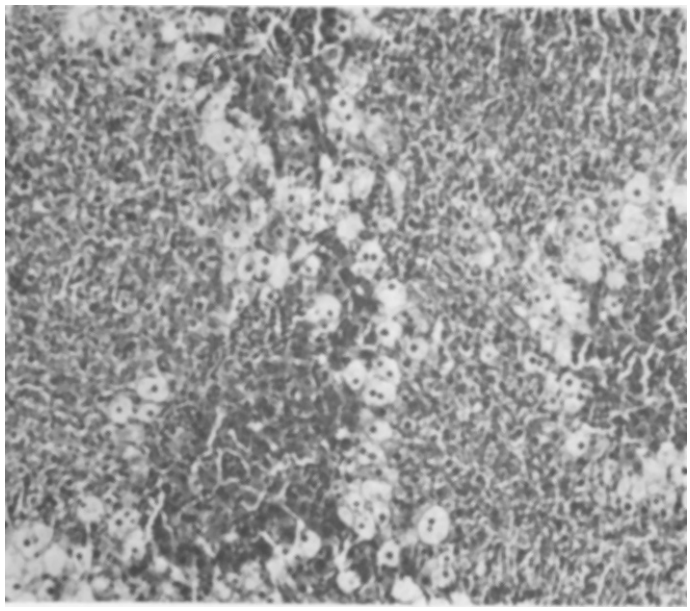
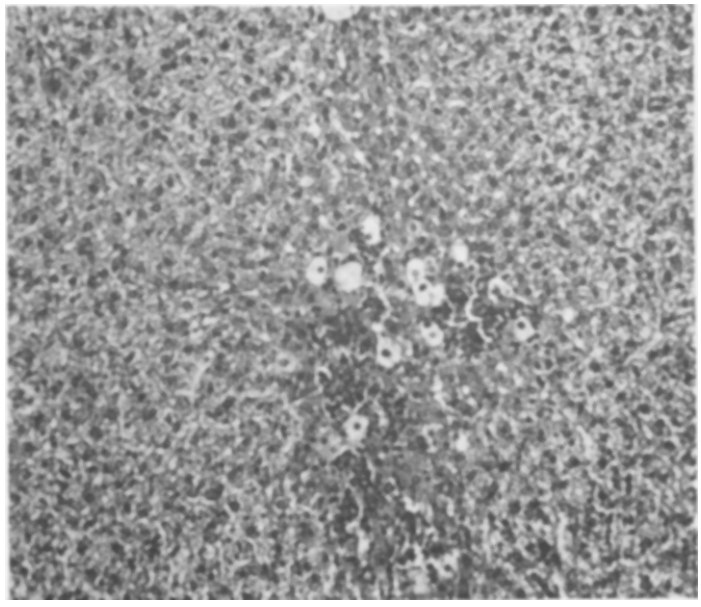
1 Brunschwig, A., Nichols, S., and Bigelow, R. R., *Arch. Path.*, 1945, **40**, 81.

2 Cameron, G. R., and Karunaratne, W. A. E., *J. Path. and Bact.*, 1936, **42**, 1.

FIG. 1.



A. Typical maximal lesions in liver of rat 24 hours after injection of .1 cc carbon tetrachloride subcutaneously. Foci of shrunken cells surrounded by markedly swollen cells.



B. "Moderate" lesion observed 24 hours after injection of carbon tetrachloride and sodium glycollate.

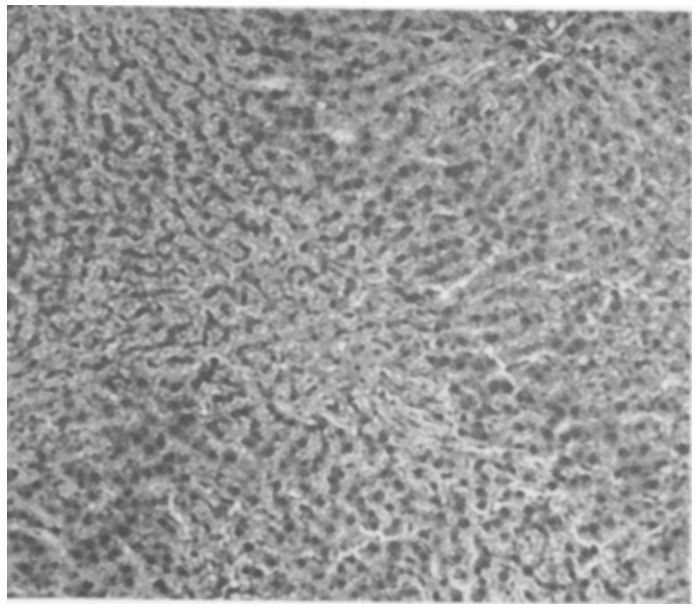


FIG. 1.
C. Minimal lesions (slight edema of some cells) after injection of carbon tetrachloride and glutathione.

mentioned compounds. Aspartic acid, glutamic acid (both as sodium salt), sodium acetate, methionine, choline alone, and choline plus cystine did not afford significant protection.

A protective action against injury by carbon tetrachloride does not necessarily depend upon the presence of –SH in the agent tested, as was the case in studies previously reported and mentioned above concerning the protective

TABLE I.
Summary of Results of Experiments on Protective Action of Various Compounds Against Hepatic Injury by Carbon Tetrachloride.

| Agent injected | No. rats | Amt. (150 g rat) | Sulphur, 150 g rat | No. showing maximal lesion | Degree of Protection. No. of rats: Moderate lesions | Degree of Protection. No. of rats: Slight or no lesions | Protection. % with moderate or no lesions |
|---|---|---|---|---|---|---|---|
| $CCl_4$ | 15 | .1 cc | — | 13 | 1 | 1 | 13 |
| $CCl_4$* + Sod. thioglycollate | 13 | 17.8 mg | 6.2 mg | 0 | 2 | 11 | 100 |
| $CCl_4$ + Sod. glycollate | 13 | 14.8 " | — | 2 | 1 | 11 | 84 |
| $CCl_4$ + Disod. thiomalate | 19 | 29.1 " | 6.2 mg | 11 | 4 | 4 | 42 |
| $CCl_4$ + Disod. malate | 14 | 26 " | — | 8 | 3 | 3 | 42 |
| $CCl_4$ + Sod. thiosulph. | 10 | 25 " | 6.2 mg | 7 | 1 | 2 | 30 |
| $CCl_4$ + Disodaspartate | 5 | 55.2 " | — | 4 | 1 | 0 | 20 |
| $CCl_4$ + Disod. glutamate | 5 | 60 " | — | 4 | 1 | 0 | 20 |
| $CCl_4$ + methionine | 19 | 60-120 mg | 12.4-24.8 | 18 | 0 | 1 | 5.3 |
| $CCl_4$ + choline | 3 | 40 mg | — | 3 | 0 | 0 | 0 |
| $CCl_4$ + choline and cystine | 8 | 30 " choline<br>25 " cystine<br>(*per os*) | 6.2 | 8 | 0 | 0 | 0 |
| $CCl_4$ + cystein | 13 | 34.5 mg | 6.2 | 8 | 2 | 3 | 38 |
| $CCl_4$ + glutathione | 10 | 60 " | 6.2 | 4 | 2 | 4 | 60 |
| $CCl_4$ + Sod. acetate | 9 | 116 " | — | 8 | 0 | 1 | 11 |

* All rats received .1 cc carbon tetrachloride per 150 g weight in addition to other injections.

action of protein and other agents against chloroform injury of the liver in dogs. The intracellular disturbances in the liver occasioned by chloroform and carbon tetrachloride intoxication respectively probably represent different phenomena. Evidence for this is the fact that a protective action was observed for both sodium thioglycollate and sodium glycollate against carbon tetrachloride injury in rats whereas in experiments in dogs with chloroform injury, sodium thioglycollate afforded protection but none was observed with sodium glycollate, indeed the liver appeared to be injured by this substance (unpublished experiments). Conversely, methionine afforded protection against chloroform injury in dogs but did not afford protection against carbon tetrachloride injury in rats.

*Summary.* Several agents were tested for protective action against carbon tetrachloride injury of the liver in rats. Marked protection was obtained with sodium thioglycollate, appreciable protection with glutathione, moderate protection with sodium thiomalate, and slight protection with cystein—all sulphydryl compounds. Sodium glycollate and sodium malate afforded protection comparable to their sulphydryl homologues. Methionine, and choline plus cystine did not afford protection. Other non-sulphydryl compounds, *i.e.*, sodium thiosulphate, aspartic acid, glutamic acid, choline, and sodium acetate afforded no protection.

A protective action against carbon tetrachloride injury of the liver in rats is not as closely related to the presence of –SH in the test agent as previously was observed for the protective action of certain compounds against hepatic injury by chloroform in the dog.

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## Blood Pressure Changes During Electronarcosis.

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The blood pressure during the first phases of electronarcosis[1] shows large and complicated variations, mainly caused by the simultaneous stimulation of the sympathetic system and the vagus nerves.[1-5] The possibility that humoral mechanisms, other than those at the autonomic nerve endings, are active in producing these pressure changes, is here considered.

*Method.* Electronarcosis was produced by applying a 60-cycle alternating current to the brain through electrodes placed on both sides of the head directly behind the eyes. As usual, a relatively high current, in most cases 150 ma, was applied for the first 30 seconds, and then decreased to about 30 ma for the rest of the electronarcosis. Rabbits were used exclusively.

Recording mercury manometers were used for the registration of the blood pressure. Fastusol[6] was used to prevent blood clotting during the recording as well as in crossed circulation experiments.

*The Blood Pressure Changes During Electronarcosis.* On starting the high initial current, the blood pressure drops due to vagus inhibition, causing arrest of the heart. After

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[2] Bikeles, G., and Zbyszewski, L., *Arch. f. d. ges. Physiol.*, 1920, **182**, 157.

[3] Ivy, A. C., and Barry, F. S., *Am. J. Physiol.*, 1932, **99**, 298.

[4] Roos, J., and Koopmans, S., *Vet. J.*, 1934, **90**, 232.

[5] van Harreveld, A., and Kok, D. J., *Arch. Néerl. de Physiol.*, 1934, **19**, 24.

[6] Modell, W., *Science*, 1939, **89**, 349.