

112 (2635)

The absorption and excretion of carbon tetrachloride in animals and in man.

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To date, the study of the toxicity of the anthelmintic dose of carbon tetrachloride has been confined to clinical observations, and to pharmacological and pathological findings. These researches have indicated that the damage to the host following the use of this drug is definitely dependent on its absorption from the intestinal tract.

Quantitative chemical methods for the study of absorption and excretion of carbon tetrachloride have been worked out in this laboratory.* The details of the methods together with a full report of the results of their application will be published elsewhere at an early date.

By the use of our methods we have been able to throw considerable light on the absorption and subsequent excretion of the anthelmintic dose of the drug in man as well as in animals. In dogs, absorption has been studied following injection of 3 cc. of the drug (the accepted therapeutic dose for dogs and for man) into loops of intestine prepared by tying off duodenum and colon under general anesthesia. The dogs were killed at intervals ranging from one to thirty hours, and the amount of carbon tetrachloride remaining in the gut determined. In this way it was shown that the whole dose is absorbed in 24 to 30 hours. The rate of absorption remains practically constant from beginning to end, though it is somewhat more rapid at first. Absorption thus determined for eighteen dogs gives data for the construction of a remarkably smooth composite curve of absorption. When 50 percent alcohol is added, up to 100 cc., there is no general tendency to increased absorption. When 97 percent alcohol is added, on the other hand, absorption is markedly accelerated during the first few hours. The addition of 10 cc. of saturated magnesium sulphate solution slightly decreases the amount absorbed.

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When the expired air of dogs is passed, for absorption, through activated charcoal, a very high percentage of the carbon tetrachloride absorbed from an intestinal loop is shown to be rapidly excreted by the lungs. In one case 96 percent of the amount lost from the gut was so recovered.

Studies of the expired air following the taking of two small doses of carbon tetrachloride by the author himself (3 cc. and 1.5-2.5 cc. respectively) show that the drug can be much more rapidly absorbed and excreted by man than by dogs. The maximum rate of excretion, which was shown in one instance to occur within 40 minutes of administration of the drug by duodenal tube, coincided with the greatest intensity of subjective sensations of dizziness and of the odor of the substance on the breath. The rate of excretion fell rapidly thereafter, following a smooth curve, which practically reached the baseline in 24 hours. The results of these experiments suggest that the rate of absorption in man depends on the concentration of the drug in the small intestine.

Another possible explanation of the rapid decrease in rate of absorption is that offered by Schultz and Marx.¹ These authors suggest, on the basis of an excellent pathological study of liver lesions produced in dogs, but on what seems to us to be inconclusive evidence, that absorption is most rapid from the duodenum, and that as the drug is carried further down the gut the rapidity of absorption decreases. That this does not seem to be the case in dogs, however, is shown by the results of our experiments, in which the rate of absorption of the drug, following injection into the duodenum, decreases only slightly at first and proceeds at a constant and relatively high rate after the first few hours.

It cannot be denied that the phenomenon of the rapid decrease in rate of absorption which apparently occurs in man might be explained by the hypothesis put forth by Schultz and Marx. Yet our experiments on man indicate that it is not always possible to draw adequate conclusions about absorption in man from the quantitative results of experiments performed on dogs. Consequently, further experiments on man will be needed before it can be settled definitely as to whether the rate of absorption de-

¹ Schultz, E. W., and Marx, Alberta, *Am. J. Trop. Med.*, 1924, iv, 469.

pend on the concentration, as our experiments up to date would lead us to believe.

It is suggested, in the light of the rôle which the concentration seems to play on absorption rate, that should the drug be administered in divided doses, the concentration reaching the tissues would be reduced and the time during which the drug remains in the intestine prolonged. By such a method of administration of the drug, the toxicity might be considerably reduced for selected patients in whom the factor of safety would outweigh that of ease of administration.

The study of the excretion of carbon tetrachloride in the expired air (which presumably occurs almost as rapidly as the drug is absorbed) seems to offer the best avenue of approach to the study of absorption of the drug in man, and of the effect of various substances that tend to accelerate or retard absorption.

113 (2636)

The determination of blood sugar.

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A method for the determination of blood sugar has been developed which is based upon the use of a more specific copper solution than has hitherto been available. Where the new procedure is employed for normal human blood the results are from fifteen to thirty percent lower than those obtained where the method of Folin and Wu is employed. Details of the procedure will be published in a short time.