

# RECENT PHARMACOLOGICAL ADVANCES IN THE COURSE OF STUDY OF CERTAIN ANTHELMINTICS<sup>1</sup>

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Although great progress has been made in the treatment and prevention of infection with intestinal parasites, there is still much work to be done in our own country and much more in many tropical and sub-tropical foreign countries. Two intestinal parasites causing great trouble and economic loss in both man and domestic animals are hookworms (*Necatur americanus*) and *Ascaris lumbricoides*. Since eggs from both these parasites must go through a period of incubation in the ground before reaching the larval stage in which they can re-infect the host or another individual, sanitary conditions which would avoid pollution of the soil with fecal matter containing the eggs would eventually eradicate the possibility of infestation with these parasites. This ultimate solution of the problem will only be slowly achieved so, in the meantime, treatment of infested individuals with drugs to rid them of parasites is a very necessary and valuable procedure.

Carbon tetrachloride was found by Hall in 1921 to be so effective in removing hookworms from an infested individual that usually only one small dose of the drug is necessary to effect a complete temporary cure of the hookworm disease. The effectiveness of this drug leaves but little to be desired and it has been used in the treatment of literally millions of cases. When used on such a tremendous scale the safety of a drug under varying conditions becomes an important factor. Except in a few occasional cases carbon tetrachloride has proved as safe as it is effective. In a few instances when alcoholics or poorly nourished individuals have been treated cases of intoxication of the host by the anthelmintic have resulted. Much work has recently been done in the department of Pharmacology at Vanderbilt in an attempt to find the cause of this occasional increased susceptibility.

Experimental work with large numbers of dogs has brought out the fact that the state of calcium nutrition is a very important factor in determining the susceptibility of these animals to carbon tetrachloride intoxication. By feeding dogs for a considerable period on a diet exclusively of lean meat, which is very low in calcium, they can almost invariably be made to show serious intoxication after doses of carbon tetrachloride which cause no symptoms in dogs on a high calcium diet. Furthermore, cases of intoxication in dogs on a low calcium diet can usually be relieved by persistent calcium therapy.

The final explanation of the preventive and curative effects of calcium cannot yet be given, but some very suggestive findings have been

<sup>1</sup>Abstract of paper presented before The Tennessee Academy of Science, November 30, 1928.

made. Using doses of carbon tetrachloride considerably larger than the anthelmintic dose it was found that a transient liver damage was produced in both protected and susceptible animals. Secondary to this liver damage there was an appearance of an unusual toxic substance, guanidine, in the blood. This increase was much more noticeable after meat was eaten but sometimes occurred in cases of severe intoxication when the animal took no food after receiving carbon tetrachloride. About the same degree of guanidine retention was seen in dogs on meat diets whether protected by calcium or not. The effects of the increase in guanidine were, however, quite different in the protected and unprotected animals. Dogs on a low calcium diet showed symptoms of nervous hyperexcitability, followed by depression, gastrointestinal irritation and a very marked fall in blood sugar to levels of extreme hypoglycemia. Dogs on a high calcium diet, on the other hand, showed almost no symptoms of intoxication and analyses of the blood showed only very slight changes in blood sugar level. Administration of calcium to intoxicated dogs restored the nervous condition to normal and tended to elevate the falling blood sugar levels.

Administration of guanidine compounds to normal animals was found to produce a condition very similar to the intoxication produced by carbon tetrachloride in symptoms and in effect on the blood sugar. Similar concentrations of guanidine were found in the blood in the two conditions and calcium salts furnished relief in both types of intoxication. We have been led to believe, therefore, that the protective effect of calcium in carbon tetrachloride intoxication lies in its antagonism to guanidine which tends to accumulate in the blood as a result of the transient interference with normal processes which may be caused by carbon tetrachloride. This work seems to emphasize the importance of insuring an adequate calcium reserve before persons are treated with carbon tetrachloride and to suggest the possible effectiveness of calcium therapy in cases of intoxication.

During the last year or two another drug, tetrachlorethylene, which is similar chemically to carbon tetrachloride, has been found to be apparently equally effective against hookworm. This drug has the advantages of being even less absorbed by the host than carbon tetrachloride and of avoiding even transient liver injury. Comparative tests of the two drugs on a large scale in actual field work will be necessary to determine which will finally prove most satisfactory.

Neither of these drugs is completely satisfactory in treating infestations with *Ascaris lumbricoides*. Oil of chenopodium is the anthelmintic in most common use against this parasite. Though a very valuable agent, it is very toxic in large doses, while the customary anthelmintic dose usually must be repeated two or three times in order to rid a person completely of parasites. An accidental overdose is usually fatal. It is hoped that a better understanding of the physiology of this *Ascaris* will lead to the discovery of a more effective and safer drug for its elimination. Such studies are already being made by other members of the department.