

series of fifty-nine syphilitics, they obtained with the lecithin test 63 per cent. positive reactions, and in twenty-four nonsyphilitics, 50 per cent. positive reactions. With sodium glycocholate there were 65 per cent. positives in syphilitics and only 17 per cent. positives in nonsyphilitics. All the precipitation reactions show in a large proportion of syphilitics an increased amount of some substance which, however, is also present in like amount in a smaller proportion of nonsyphilitics. The fixation of complement by the combined action of syphilitic serum and extract of liver or heart remains the only property of syphilitic serum thus far discovered that is not shared by so large a percentage of nonsyphilitics as to preclude its use for diagnosis.

CONCLUSIONS

1. The Bruck precipitation test for syphilis fails in a considerable percentage of early secondary syphilis.
2. It gives positive reactions in from 24 to 28 per cent. of nonsyphilitics.

THE PHARMACOLOGY OF THE OIL OF CHENOPODIUM

WITH SUGGESTIONS FOR THE PREVENTION AND TREATMENT OF POISONING *

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The oil of chenopodium is an essential oil which is distilled from American wormseed or Jerusalem oak, a weed quite common in Maryland and in the states farther south. It first came into use in therapeutics in the treatment of ascariasis, but in recent years it has also become the chief remedy against ankylostomiasis, and is at present practically the only drug used for the eradication of this disease. As shown in the reports of the International Health Commission,¹ the number of patients treated with the oil of chenopodium is very large. It has been employed in several million cases of hookworm in the last few years.² Its behavior in the body is therefore a matter of considerable interest, not only to the pharmacologist, but also to those specially interested in the treatment of hookworm and other intestinal parasites. The obvious necessity of making the information concerning its action readily available suggested to me the advisability of presenting this summary of the results of pharmacologic investigations.

PHYSIOLOGIC ACTION

That the action of oil of chenopodium is not confined to the effect on the organisms against which it is directed has been established by experiments on animals. Brüning³ was the first to call attention to its toxicity by tests on different animals, but the action of the drug has since been made the subject of more extensive investigation in this laboratory. Nelson and myself⁴ have shown that oil of chenopodium is a strong local irritant, causing severe inflammation of the mucous membranes. Even very small quantities may prove very toxic and cause death when given to different animals. One-half c.c. of the oil given by mouth to a medium-sized rabbit produced symptoms of

severe poisoning, such as vomiting, convulsions, coma, paralysis, and death. The active dose was smaller for cats, 0.2 c.c. per kilogram of oil of chenopodium being toxic, and 0.25 c.c. per kilogram proved fatal. Dogs were much more resistant than cats, but severe symptoms of poisoning were likewise observed in these animals. Of particular importance is the observation we made that a dose which is not effective at first may cause serious symptoms and death when repeated within one or several days. We noticed that sensitiveness to the oil of chenopodium persisted for from five to nine days. This is well worth remembering when the dose has to be repeated, as is sometimes the case, in the treatment of hookworm, for the first dose may not prove efficacious and a second or third dose is required to accomplish the desired result. Attention was also called to the effect of the nutritional condition and of diet on the toxicity of the oil. Fasting or poorly nourished animals succumbed to much smaller doses. The resistance was noticeably greater, on the other hand, in animals that had been receiving a rich carbohydrate diet for several days before the oil was given, or when the administration of the oil of chenopodium was preceded by a sufficient quantity of fatty oil, such as olive oil, coconut oil, or castor oil. Quantities which invariably caused death were survived without the production of symptoms of poisoning when any of these oils were given shortly before or after the administration of oil of chenopodium. Very satisfactory results were also obtained when several doses of about 15 c.c. of the fatty oils were given during two or three days preceding its administration. That disturbance of renal function may be caused was shown in experiments in which the permeability of the kidney was tested after the administration of the oil of chenopodium, for Bengis and myself⁵ observed that fat-soluble dyes injected subcutaneously or when fed by mouth failed in some cases to be eliminated in the urine of rabbits under these conditions. Its effect on the kidney was further illustrated in another series of experiments in which evidence was obtained indicating that under certain conditions it may cause renal irritation, even when combined with some substances that were otherwise its physiologic antagonists. Albumin and casts were frequently found when it was given in an emulsion in acacia to rabbits. But when oil of chenopodium was dissolved in one of the fatty oils which, as previously mentioned, decreased the general toxicity of oil of chenopodium, renal irritation became more marked. This, as indicated in a recent report⁶ from this laboratory, is probably due to the combined action of the two, that is, the oil of chenopodium and the fatty oil each producing renal irritation, the effect being enhanced when both were given together. It is important to point out in this connection that this does not apply with equal force to carnivorous animals, as the same amounts of oil of chenopodium and coconut oil fed to cats seldom produced these results.

Its poisonous nature was also shown by the tendency to cause depression of the circulation and respiration, as well as to lessen the intestinal movements. In experiments on different animals under anesthesia it was observed that blood pressure may fall considerably in some instances, as 0.02 c.c. of oil of chenopodium per kilogram when injected intravenously may

* From the Pharmacologic Laboratory, Bureau of Chemistry, U. S. Department of Agriculture, Washington, D. C.

1. Report Int. Health Com., Washington, D. C., 1915.

2. Personal communication from Dr. Victor Heiser.

3. Brüning, H.: Ztschr. f. exper. Path. u. Therap., 1906, **3**, 564.

4. Salant, W., and Nelson, E. K.: Am. Jour. Physiol., 1915, **36**, 440.

5. Salant, W., and Bengis, R.: Jour. Biol. Chem., 1916, **27**, 403.

6. Salant, W., and Bengis, R.: Jour. Pharmacol. and Exper. Therap., 1917, **9**, 529.

be followed by a fall of blood pressure amounting to 40 or 50 per cent.⁷ Although this was not the rule, it is well to bear in mind that it occurred with sufficient frequency to serve as a warning to the clinician of the nature of the drug he is prescribing. Evidence was obtained that the action might be due to direct effect on the heart. This was also shown in an extensive series of experiments on the isolated frog heart.⁸ Very small quantities proved to be quite active, as one minim of the oil of chenopodium to 100 c.c. of Ringer's fluid, when perfused through a normal frog heart, produced marked depression and sometimes arrest of the heart in diastole. In numerous observations on different animals under chloretone or morphin-ether anesthesia it was also noticed that respiration may be depressed or even completely inhibited⁹ when the oil of chenopodium is injected intravenously in the form of an emulsion. That the oil of chenopodium is a general depressant is further shown by the effect produced on peristalsis.¹⁰ The movements of the isolated intestines in intact animals may be inhibited by the oil of chenopodium. According to Muirhead and Gerald¹¹ uterine contraction may likewise be inhibited if the isolated organ is exposed to the oil, provided, however, the concentration is not too low.

Little is known of its fate in the body, but it might be inferred by analogy that, like other essential oils, it is conjugated with glycuronic acids. It is apparently not eliminated uncombined in the urine or in the bile for its odor in these fluids was never detected. On the other hand, its elimination by the lungs¹² was observed in experiments on animals after its intravenous administration, for the characteristic odor in the expired air was unmistakable. It is evident, therefore, from the experimental data cited above, that the drug is very active. That this also holds for human subjects is shown by the incidence of poisoning with this drug. Levy¹³ reported twelve cases, nine of which were fatal. Coutant¹⁴ reported recently one case of severe poisoning, but the patient recovered. I have been informed of several cases that have come under the observation of the medical officers of the International Health Commission.¹⁵ The substance under consideration should therefore be handled with caution when used for internal medication as it has a tendency to affect the central nervous system, the heart, respiration, digestive organs, and the kidneys. In the presence of renal or cardiac disorders the oil of chenopodium should be given in small doses only, while in advanced cases of chronic nephritis or heart disease its use would seem to be altogether contraindicated.

As the liver undoubtedly plays an important part in detoxifying the oil of chenopodium while abnormal changes in the gastric and intestinal mucosa may accelerate its absorption into the circulation, it may be expected that in hepatic and gastro-intestinal diseases it may likewise prove more toxic. The impor-

tance of the nutritional condition in determining the toxicity of oil of chenopodium has been established by experiments on animals, as has been sufficiently indicated. This applies also to human beings. The case reported by Coutant furnishes evidence of the effects of the drug when administered to the poorly nourished and weak individual. Two doses of 10 minims each given in twenty-four hours were toxic, but the patient was 21 years of age and weighed only 95 pounds.

TREATMENT OF POISONING

Since cases of poisoning are sure to occur, the question of treatment deserves consideration. When large doses have been swallowed lavage may be resorted to with beneficial results. If carried out promptly after the oil is taken it may prove effective in preventing serious consequences, since absorption of the oil from the stomach is slow. In experiments that Livingston and I¹⁶ carried out we often found that several hours may elapse before evidence of absorption into the circulation could be obtained, when the oil was introduced into the stomach of animals, the pylorus having been ligated previously.

The importance of not delaying lavage too long after the poison has been swallowed is further emphasized by the fact that absorption from the duodenum was found, on the contrary, to be very rapid. In some of the experiments in this laboratory the introduction of oil of chenopodium was followed by the immediate appearance of the characteristic effect on the circulation.

No chemical antidote has yet been found. The treatment in cases of poisoning would, therefore, be symptomatic. Stimulation of the respiratory and the circulatory systems would undoubtedly be of value. In experiments on the isolated heart, we found that digitalis and epinephrin are excellent antagonists. The stimulating action of digitalis has been found to be very persistent, and may completely overcome the depression caused by the oil. Caffein was also tried out. It, on the contrary, aided the action of the oil of chenopodium. Heart action ceased altogether when perfusion with caffein followed treatment with chenopodium. The action of caffein in poisoning with chenopodium may be different, however, in intact animals, and is being investigated in this laboratory.

While oil of chenopodium may be regarded as a safe remedy for patients in good physical condition, it should be used very cautiously in poorly nourished and weak or neurotic individuals. A diet containing a liberal amount of fats and carbohydrates, fed at least for several days before the treatment is instituted, may render the drug much safer. The routine administration of large doses of castor oil before and soon after oil of chenopodium, as recommended by Hall and Foster,¹⁷ should be given serious consideration, as it may prove to be of prophylactic value.

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17. Hall, M. C., and Foster, W. D.: *Oil of Chenopodium and Chloroform as Anthelmintics*, *THE JOURNAL A. M. A.*, June 30, 1917, p. 1961.

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8. Salant, W., and Livingston, A. E.: *Am. Jour. Physiol.*, 1916, **41**, 21.

9. Salant, W., and Livingston, A. E.: *Am. Jour. Physiol.*, 1915, **38**, 67.

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11. Muirhead, A. L., and Gerald, H. F.: *Jour. Pharmacol. and Exper. Therap.*, 1916, **8**, 253.

12. Salant, W., and Livingston, A. E.: *Proc. Soc. Exper. Biol. and Med.*, 1915, **12**, 132.

13. Levy, R. L.: *Oil of Chenopodium in the Treatment of Hookworm Infections*, *THE JOURNAL A. M. A.*, Nov. 28, 1914, p. 1946.

14. Coutant, A. E.: *Chenopodium Poisoning*, *THE JOURNAL A. M. A.*, Nov. 25, 1916, p. 1599.

15. Personal communication from Dr. Victor Heiser.

Acute Intestinal Troubles in Germany.—The *Nederlandsch Tijdschrift* quotes from J. Schwalbe in the *Deutsche medizinische Wochenschrift*, No. 33, that diarrhea is prevalent, especially in northern Germany. He has been making a collective inquiry on the subject, and states that on account of the lack of bacteriologic examination it is impossible to say to what extent contagion is involved, but that in any event the bread and the poor quality of the food have certainly not a little to do with it.