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An Effective Ascaricide-Hexylresorcinol.

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Ascariasis is a condition which has been recognized since the earliest medical times, and although it may cause little apparent disturbance the parasites are always a potential source of danger from migration into the various body cavities, from mechanical obstruction of ducts, the air passages, or the intestines, and from chemical intoxication. Between the latitudes of 35° North and 30° South there is a belt of ascariasis around the entire world. In the rural population of certain states of this country which lie in this belt, there is an incidence in certain areas as high as 48%,[1] while in other countries, such as China, as many as 90% of the population of certain regions have been found to be infested with these parasites. A great many substances and concoctions have been used for the removal of these worms, but they have all proven to be either inactive or dangerous. The two in most common use at present are Santonin and Oil of Chenopodium (or its active principle, Ascaridol). Both of these substances have been given to many thousands of patients without intoxication. On the other hand many sudden unexplained deaths have followed their use, which makes it impossible to predict what will be the outcome of their administration. Carbon tetrachloride and tetrachlorethylene, which are both very efficient against hookworm, are relatively ineffective against ascaris and may cause dangerous migration of these parasites.[2] We have, therefore, no safe or effective means of removing ascaris. On this account a search for a non-toxic ascaricide was begun several years ago in this laboratory, and a great number of experiments have been carried out on the physiology and pharmacology of this parasite. Several active substances which might be of practical value have been found by us, among which hexylresorcinol seems most nearly to fulfill the necessary requirements of an ideal ascaricide.

Hexylresorcinol is a white, waxy, crystalline substance. That which we have used in these experiments was kindly given us by Dr. Veader Leonard and had a melting point of 59°-61°C. It is only slightly soluble in water or mineral oil but readily soluble in alco-

[1] Cort, W. W., Otto, G. F., and Spindler, L. A., *South. Med. J.*, 1929, xxii, 608.

[2] Lamson, P. D., Minot, A. S., and Robbins, B. H., *J. Am. Med. Assn.*, 1928, xc, 345.

hol, glycerin and vegetable oils. It has been shown by Leonard to have an extraordinarily high bactericidal action and to be the least toxic of a large series of substituted resorcinols which he has studied.[3] It has been given as the pure crystals in gelatin capsules by mouth in doses varying from 0.1 to 1.0 gm. 3 times a day to individuals for periods of as much as 10 weeks without any deleterious effect,[4] and to many hundreds of patients in olive oil under the name of Caprokol (N.N.R.) as a urinary antiseptic.[5] It has been shown by us to be extremely active in great dilution on the pig ascaris *(Ascaris suum) in vitro* in several hundred experiments; to remove 100% of the ascaris in 16 out of 17 dogs as shown by autopsy, and when given in 1 gm. doses in gelatin capsules to 20 patients harboring ascaris to have removed from 90% to 100% of these parasites, as shown by carefully controlled egg counts. One hundred human cases of ascariasis have been carefully studied and controlled by egg counts before and after the administration of hexylresorcinol in varying amounts, and given in different ways. The results of these experiments will be reported later as well as comparative studies of other resorcinols.

Crystalline hexylresorcinol has irritant properties. It causes a burning sensation of the tongue, followed by an anesthetic action. The crystals, aqueous solutions, or mineral oil suspensions, all give this burning sensation in the mouth and are unpalatable. Although this burning sensation on the tongue can be largely overcome by dissolving the hexylresorcinol in vegetable oils, our experiments show that the action of hexylresorcinol on ascaris *in vitro* is greatly decreased when dissolved in such a solvent. For example, 0.1% hexylresorcinol in water will kill *Ascaris suum in vitro* in 2 minutes, while it takes 20 minutes or more to kill these parasites in a 3% olive oil solution.

Although these purely experimental administrations of one gram of hexylresorcinol crystals in hard gelatin capsules to adults and one-half gram to children followed by mineral oil have been extremely efficient in removing ascaris from dogs and man, the therapeutic dose and best mode of administration remain to be worked out.

The general feeling has been that one must have a vermifuge which would remove all the worms in a single dose. This is important when elaborate preparations for treatment must be made, and

[3] Leonard, Veader, *Science*, 1925, lxii, 408.

[4] Leonard, Veader, *J. Urol.*, 1924, xii, 585.

[5] Leonard, Veader, and Wood, Austin, *J. Am. Med. Assn.*, 1925, lxxxv, 1855.

where there is danger of intoxication. If, however, as is the case with hexylresorcinol, no preparation of the patient is necessary except to take the drug in the morning on an empty stomach and to wait an hour or so before eating to let the drug come in better contact with the parasites, there is no reason why the drug should not be repeated if necessary.

It should be pointed out that although hexylresorcinol crystals have been given by Leonard to many individuals and by us to between 50 and 100 patients without symptoms of any kind and have also been taken by us with nothing more than a burning sensation in the stomach, this may cause gastric irritation. In dogs this varies from a general reddening of the gastric mucosa to small submucal hemorrhages, and even necrosis of the epithelium in places. Microscopic sections show, however, that these lesions are entirely superficial. Examination of the gastro-intestinal tract of dogs 3 days or more after the administration of hexylresorcinol crystals shows no evidence whatever of any lesion having been produced. The fact that hexylresorcinol is a strong protein precipitant leads us to believe that it will not penetrate deeply into the tissues. Microscopic examination shows that this is the case and the rapid healing of these lesions, and absence of symptoms in patients having been given this substance in large amounts over long periods of time confirm this belief. If, however, alcohol is taken together with hexylresorcinol, this acts as a solvent and carries the substance deeply into the tissues. Here there is danger of serious damage to the epithelium and alcohol should be strictly avoided when taking hexylresorcinol.

Since an olive oil solution of hexylresorcinol is not a suitable form of administration as an ascaricide, the question naturally arises as to whether one should consider it safe to give the crystals which may cause gastric irritation. Further experimentation may produce a method of administering crystalline hexylresorcinol which will allow it to act on the parasites without causing irritation of the mucosa but it is far safer to consider that such irritation may occur rather than to disregard it. If one considers the action of most drugs it will be seen that our confidence in them is based on the results of their action rather than on our knowledge of how they act. The effect of ether, for example, on the body tissues is invisible yet the functional changes are profound. Consciousness is completely obliterated, an extreme acidosis is produced, as well as hyperglycemia, etc. Its use is justified only because experience has shown that recovery takes place without permanent harm. One also submits to all manner of physical injuries such as sunburn, operations on vital

organs, etc., knowing that regeneration will take place without permanent injury. We feel justified, therefore, in suggesting crystalline hexylresorcinol as an ascaricide in spite of its irritant properties, because we feel that it is exceptionally effective, it kills rather than anesthetizing the parasites, thus reducing the danger of migration, its irritant action, which should theoretically be merely superficial, has been shown by experiment to be so, and finally because hundreds of patients have taken this substance in olive oil solution as a urinary antiseptic in much greater amounts than we suggest for ascariasis without known complications. When given as an ascaricide, it should be taken on an empty stomach to prevent the possibility of its combination with the proteins of the food. Although Leonard has been unable to show any pathological changes after its long continued use the general pharmacology of this substance remains to be worked out.

We wish to express our gratitude to the International Health Division of the Rockefeller Foundation for their generous support of this work, to Mrs. Elfreda Caldwell for her help in the clinical studies, to Dr. E. L. McCafferty and Dr. W. D. Partlow of the Bryce and Searcy Hospitals, Alabama, and finally to Dr. E. L. Bishop, Commissioner of Health for the State of Tennessee, and Dr. F. B. Clark of Gainsboro, Tennessee, for their kindness in making arrangements for the clinical study of this drug.

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The Accumulation of Iron in Tuberculous Areas.

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In previous communications[1, 2, 3] it was shown that a vital dye, trypan blue, or a metal in the form of its salt, ferric chloride, when injected into the circulating blood stream rapidly accumulates in an area of inflammation, where the substance is fixed and fails to drain to the tributary lymph nodes.

Bowman, Winternitz, and Evans by microscopic studies[4] found

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1 Menkin, V., *J. Exp. Med.*, 1929, l, 171.

2 Menkin, V., *J. Exp. Med.*, 1930, li, 879.

3 Menkin, V., and Menkin, M. F., *J. Exp. Med.*, 1930, li, 285.

4 Bowman, F. B., Winternitz, M. C., and Evans, H. M., *Centralbl. Bakteriol.*, 1912, lxv, 403.