Evaluation of Hetrazan As an Anthelmintic In Children

By MILDRED B. GABBARD, M.D., EMIL KOTCHER, Sc.D., and E. D. PULLIAM, M.S.P.H.

DESPITE some 40 years of effort to eradicate intestinal helminthic infestation in man, the problem is still one of considerable magnitude in certain mountain areas of Kentucky. The situation has improved, as shown by the data in the accompanying table for Breathitt, Leslie, and Perry Counties. In Owsley County, Ky., however, a survey in early 1952 of 151 children, the majority of school age, revealed that 76.8 percent were infested with *Ascaris lumbricoides;* 56.2 percent, with *Trichuris trichiura;* and 29.1 percent, with hookworm.

Attempts to reduce the incidence of intestinal parasitic infestation in southeastern United States began in 1913 and 1914 with mass treatment programs carried out by the Rockefeller Sanitary Commission for the Eradication of Hookworm. Following a report by Otto and Cort in 1934 (*1*), which showed poor sanitation to be a basic factor in the perpetuation of ascariasis, mass treatment programs largely fell into disuse, and emphasis was given to privy-building campaigns and health education. The studies by Otto and Cort showed that reinfestation occurred within 8 months to 1 year if sanitation and sanitary habits were not improved.

For the past 20 years, sanitarians have worked diligently at convincing property owners to construct satisfactory fecal disposal systems, but, even when construction has been provided free, the programs have not been entirely successful because some families could not afford the cost of the materials. And even when sanitary facilities have been constructed, use has not been made of them in many instances because of cultural habits.

Coordinated Attack

In order to impress the families in Owsley County who had high infestation rates for hookworm and *Ascaris* with the need for better sanitary facilities, a coordinated attack on the problem was decided upon: treatment, health education, and privy construction.

Stool examinations of 396 school children were made to determine what parasites were present, and a vermifuge was given to the persons found infested. Instruction on the life cycle of intestinal helminths and their pathological capabilities was given to school children and to a few adult groups. Finally, the families were contacted and advised as to their sanitation needs, and they were offered aid in constructing privies and other sanitary facilities.

The compound 1-diethylcarbamyl-4-methylpiperazine dihydrogen citrate (Hetrazan) was selected as the vermifuge because it is relatively nontoxic and because *Ascaris* was the most prevalent helminth. Reports by a number of investigators on the efficacy of this drug as an ascaricide have indicated cure rates varying from 33.3 percent to 80 percent (*2–9*). The differences could be attributed to variations in the dosages and regimens used in treatment, variations in the fecal examination techniques

Dr. Gabbard, regional medical consultant with the Kentucky State Department of Health since 1953, was health officer of Lee and Owsley Counties, Ky., when the study reported here was made. Dr. Kotcher, now on leave of absence to serve as public health laboratory consultant with the United States Operations Mission in Vietnam, has been associate professor of microbiology at the University of Louisville School of Medicine since 1947. Mr. Pulliam was engaged in communicable disease control work with the Kentucky State Department of Health during 1952 and 1953 and is now supervisor of the department's home accident prevention section.

and time intervals employed in determining cures, variations in the age of the patients in the study groups and in the number of patients in each group, or, possibly, variations in the strains of *A. lumbricoides* found in different parts of the world.

In view of the varied results and procedures associated with this drug and the possibility of differences in strain susceptibility, it was decided to collect data on the efficacy of the drug as it was used in the Owsley County program. The study was sponsored by the department of microbiology, University of Louisville School of Medicine, and the Kentucky State Department of Health. It was supported in part by the Medical Research Grant of the Commonwealth of Kentucky.

Examination and Treatment Methods

The first group in Owsley County treated with the drug consisted of 81 white school children, a few of whom were less than 6 years of age. The following dosages of the drug with water were given to the children at the school during the school day (6 hours): one 100-mg. tablet 3 times a day for 5 days to children aged 1 through 6 years; two 100-mg. tablets 3 times a day for 5 days to children aged 7 through 10 years; and three 100-mg. tablets 3 times a day for 5 days to children over 10 years of age. The student's daily routine was not interrupted in any way except for the actual administration of the drug. Fecal specimens were examined by zinc sulfate flotation and direct smear techniques before treatment and 1 to 2 weeks after treatment.

A second group from the same county consisted of 68 white school children. Each child in this group was given 12 mg. of the drug per pound body weight in 3 divided doses the first day. When toxic symptoms appeared among some of the children, the dosage was decreased to 6 mg. per pound of body weight, and this amount was administered in 3 divided doses each day for the next 4 days. Feces were examined before treatment, 2 to 3 weeks after treatment, and again 3 to 4 weeks after treatment, using the same techniques used for the first group.

The toxic symptoms probably would not have appeared with the 12-mg. dosage if the 3 doses could have been given at 6-hour intervals instead of at 3-hour intervals, for the few children who were given doses at home did not show such symptoms. Since the vermifuge had to be administered during the 6-hour school day, the smaller dosage became necessary.

The vermifuge did not kill the worms. It started a churning action inside the child, and in some instances the worms were vomited and in others they were expelled by way of the rectum. All the children got excellent results, some of them passing as many as 80 to 100 worms after one treatment.

Comparison of *Ascaris* infestation rates in selected counties of Kentucky, prior to 1921, in 1928–30, and in 1950

County	Prior to 1921 [1]		1928–30 [1]		1950	
	Number examined	Percentage positive	Number examined	Percentage positive	Number examined	Percentage positive
Breathitt	1, 871	34. 6	872	68. 3	212	32. 5
Leslie	2, 492	70. 6	824	67. 0	479	17. 7
Perry	2, 197	54. 1	934	33. 2	376	25. 0

[1] Reference 1.

Examination Results

According to examination of fecal specimens from the first group of children before treatment, all were infested with *A. lumbricoides;* 68, with *T. trichiura;* and 33, with hookworm. Post-treatment examinations revealed that 34 (41.9 percent) of the children were negative for *Ascaris* ova; 27 (39.8 percent of those infested with *T. trichiura*) were negative for *Trichuris* ova; and 2 (6.6 percent of those infested with hookworm) were negative for hookworm ova.

Post-treatment examination of the children in the second group, who received somewhat larger doses of the drug than the children in the first group, showed that 36, or 52.9 percent, were negative for *Ascaris* ova in their feces 2 to 3 weeks after treatment. Only 18, or 26.5 percent, of the children in this group, however, were negative 3 to 4 weeks after treatment. Not enough of the children in the second group

were infested with *Trichuris* or hookworm for evaluation of the efficacy of the drug on these helminths.

Evaluation of Results

The difficulty of evaluating precisely an anthelmintic drug when it is administered to ambulatory patients is recognized. The possibility that the positive results of examinations made even 1 to 2 weeks after treatment represent reinfections must be considered, although the possibility is very remote. This study, however, was made specifically to determine whether or not Hetrazan is a safe and useful drug for treating school children at school, and the results were evaluated on this basis.

The results obtained in Owsley County in cases of *T. trichiura* and hookworm infestation are comparable to those reported by Hoekenga in his Honduran studies (*8*). The drug has relatively little effect on the hookworm, and it is not a very efficacious compound against *T. trichiura*, although the percentage of cures among the children infested with this helminth was much higher than the percentage among the children infested with hookworm.

The results obtained in the cases of ascariasis indicate that post-treatment examination of the patient should be at an interval greater than 2 or 3 weeks. It appears that the drug may merely suppress egg production, as indicated in the report by Oliver-Gonzalez and his associates (*2*), and not eradicate the worm. (Many of the children, however, did pass worms, as noted above.) It is quite probable that many of the children in the second group who were negative in the first post-treatment examination and positive in the second examination were so because egg production had been suppressed by the drug. Hoekenga (*9*) commented on this suppressive effect in his Honduran studies.

Although the drug used in this study does not compare favorably with other drugs in its ability to cure a high percentage of cases of ascariasis, it does have the advantage of being less toxic. It does not cause mucosal burns of the mouth, and the patient is not required to fast and to undergo saline purgation before taking it. Further studies should be made to determine whether several treatments, at monthly intervals, with a smaller dosage of this drug or a single treatment with a larger dosage over a longer period of time will effect as many cures as more efficacious compounds.

Summary

A campaign against intestinal helminthic infestation in Owsley County, Ky., included treatment of infested school children with 1-diethylcarbamyl-4-methylpiperazine dihydrogen citrate (Hetrazan), health education, and aid in constructing sanitary fecal disposal facilities.

When given in amounts of 6 mg. per pound of body weight in 3 divided doses for 4 days, the drug caused elimination of *Ascaris lumbricoides*. The early favorable results, as determined by examination of feces during the second and third weeks after treatment, were appreciably lessened when examinations were performed during the third and fourth weeks after treatment, the percentage of "cures" decreasing from 52.9 to 26.5.

The drug had some effect in eliminating *Trichuris trichiura*, but much less effect in eliminating hookworms, as indicated by post-treatment examination of feces for ova.

EDITOR'S NOTE: The use of the trade name Hetrazan in this paper is for identification only and does not represent an endorsement of the drug by the Public Health Service. Hetrazan was supplied by Lederle Laboratories Division, American Cyanamid Company.

REFERENCES

(*1*) Otto, G. F., and Cort, W. W.: The distribution and epidemiology of human ascariasis in the United States. Am. J. Hyg. 19: 657–712 (1934).

(*2*) Oliver-Gonzalez, J., Santiago-Stevenson, D., and Hewitt, R. I.: Treatment of six cases of ascariasis in man with 1-diethylcarbamyl-4-methylpiperazine hydrochloride. South. M. J. 42: 65–66 (1949).

(*3*) Garcia, E. Y.: The "Hetrazan" treatment of ascariasis among Filipinos. The Medical Reporter (Philippine Islands) 2: 1–4 (1949).

(*4*) Etteldorf, J. N., and Crawford, L. V.: Treatment of ascariasis in children; use of 1-diethylcarbamyl-4-methyl piperazine dihydrogen citrate (Hetrazan). J.A.M.A. 1943: 797–799 (1950).

(5) Loughlin, E. H., Joseph, A. A., Rappaport, I., and Nullin, W. G.: Treatment of human ascariasis with Hetrazan. Lancet 261: 1197–1200 (1951).
(6) Wanson, M.: Essai de traitement curatif de la filariose à *Loa loa* et de la filariose apériodique par les dérivés de la pipérazine. Ann. Soc. Belge. Med. Trop. 29: 73–80 (1949).
(7) Colbourne, M. J.: Unsuccessful treatment of ascariasis with Hetrazan. Lancet 258: 996 (1950).
(8) Hoekenga, M. T.: Treatment of ascariasis with 1-diethylcarbamyl-4-methlypiperazine hydrochloride. South. M. J. 44: 1125–27 (1951).
(9) Hoekenga, M. T.: Treatment of ascariasis in children with Hetrazan syrup. Am. J. Trop. Med. & Hyg. 1: 688–692 (1952).