THE THERAPEUTIC VALUE OF TWO NEW SULFONAMIDE COMPOUNDS, SUCCINYLSULFATHIAZOLE AND PHTHALYLSULFATHIAZOLE, IN EXPERIMENTAL TRICHINOSIS*

DONALD L. AUGUSTINE, ScD.†

BOSTON

DESPITE the wide and successful use of sulfonamide compounds in the treatment of bacterial infections, they have not been found to be particularly promising as therapeutic agents in diseases caused by animal parasites. It must be admitted, however, that present knowledge of the value of these drugs in the treatment of parasitic diseases has scarcely advanced beyond the experimental stage. It has been shown that sulfanilamide is a complete sterilizing agent against the malarial parasite *Plasmodium knowlesi* in rhesus monkeys, but it is not usually effective in human malaria due to *P. vivax*,[1] whereas both promin and sulfadiazine are definitely active against the three common species of human malaria.[2] Encouraging results have been obtained with sulfaguanidine used to combat coccidiosis in chicks,[3] lambs[4] and calves.[5] Critical tests with sulfanilamide derivatives against amebic infections have not been performed. Fairley,[6] however, noted that amebic ulcers heal during sulfaguanidine therapy, but that they relapse after cessation of treatment. Keil[7] observed no effect on the numbers of bancroftian microfilariae in the blood of 9 lepers treated with Prontosil. McCoy[8] found sulfanilamide to be entirely ineffective in the treatment of trichinosis in rats.

At the present time there is no specific treatment for trichinosis. Constant world-wide search has utterly failed to find an anthelmintic that will remove the adult worms from the intestinal tract or destroy the larvae in the blood stream and muscles.

The physical properties of two new sulfonamide compounds, succinylsulfathiazole (sulfasuxidine) and phthalylsulfathiazole (sulfathalidine), are such that they suggest possible anthelmintic activity. Both are sparingly absorbed from the gastrointestinal tract, and a high concentration can be maintained in the diseased intestine without causing untoward toxic manifestations.[9, 10] They have extremely high bacteriostatic properties, their action being essentially limited to the local effect on the contents of the gastrointestinal canal.[11] It therefore seemed important to determine whether these drugs also had anthelmintic properties in trichinosis, especially against the intestinal stages of the parasite.

The tests with both drugs were similar. A single experiment was made for each drug in the following manner:

Five guinea pigs, each weighing approximately 260 gm., were forcibly fed approximately 3000 infective Trichinella larvae. Two days later, at which time the worms had approached sexual activity in the small intestine,[12] treatment of 3 of the animals was started. Food was withheld for fifteen hours prior to treatment, but was replaced again after the first administration of the drugs. Each of the 3 treated guinea pigs received by a stomach tube at 9 a.m., noon, 3 p.m. and 6 p.m., on two consecutive days, 0.5 gm. of one or the other of the drugs‡ suspended in 1 cc. of water. Three days after treatment was begun, or five days after the infective feeding, 1 of the untreated and 2 of the treated animals were sacrificed and their intestines examined for adult parasites. The remaining animals, 1 untreated and 1 treated, were sacrificed thirty days after receiving the infective larvae. Direct microscopic examinations for encapsulated trichinae were made on bits of masseter and diaphragm muscles pressed between two glass slides.

The dosage used was arbitrarily determined. Poth and Knotts[9] fed dogs 1 gm. of succinylsulfathiazole per kilogram of body weight daily in six divided doses for ninety-five days without the development of toxic manifestations. A marked lowering of the number of coliform bacteria occurred after twenty-four hours and persisted throughout the experiment. According to Poth and Ross[10] phthalylsulfathiazole has two to four times the bacteriostatic activity of succinylsulfathiazole. It is believed, therefore, that our dosage, approximately 8 gm. per kilogram a day for two consecutive days, was adequate to demonstrate any trichinicidal effect of these drugs.

The results obtained from both drugs were essentially the same. No deaths occurred among the untreated and treated animals. The untreated animals showed no signs of trichinosis. Loss of appetite, loss of weight and transient soft stools were characteristic developments among all the treated animals. These were believed to be toxic manifestations of the drugs.

Adult worms were equally numerous in the intestines of both untreated and treated animals. The worms were alive and normally active, and the females were gravid with living embryos. Both animals sacrificed thirty days after infection appeared equally parasitized with encapsulated trichinae. Thus, no evidence was obtained that either succinylsulfathiazole or phthalylsulfathiazole has any value in the treatment of trichinosis.

SUMMARY

The effect of two new sulfonamide compounds, succinylsulfathiazole and phthalylsulfathiazole, in the treatment of experimental trichinosis is described.

The experiment showed that neither succinylsulfathiazole nor phthalylsulfathiazole is of any value in the treatment of trichinosis.

*From the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School and Harvard School of Public Health.

†Associate professor of comparative pathology and tropical medicine, Harvard Medical School and Harvard School of Public Health.

‡The compounds for this test were supplied by Sharp and Dohme, Incorporated, Philadelphia.

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MEDICAL PROGRESS

MALARIA IN MASSACHUSETTS

VLADO A. GETTING, M.D., DR.P.H.*

BOSTON

MALARIA has been known to exist in Massachusetts from the earliest colonial times. Unfortunately, the malarial parasite and the transmission of malaria by mosquitoes were not discovered until the latter part of the nineteenth century. Consequently, it is difficult to determine the magnitude of the malaria problem in Massachusetts previous to that time, since many clinical entities were confused because of the lack of diagnostic refinements. There is, however, a certain amount of information concerning the prevalence of intermittent fever, ague, bilious fever, malignant fever, pond fever or mortal fever, as malaria was variously called in earlier times. Perhaps the completest early account of malaria in Massachusetts is to be found in the Boylston Prize Dissertations of 1836, in which Oliver Wendell Holmes[1] presented a paper entitled "Indigenous Intermittent Fever in New England." This paper was based on a review of the previous writings on the subject and personal communications from physicians.

From his search among the early writings on medical history in New England, Holmes concluded that intermittent fever existed in at least several places in New England but that the records of its existence in the literature were scanty and inaccurate. The second portion of his paper consists of replies to inquiries that he had sent to physicians throughout New England. This method of surveying the malaria situation was more fruitful, and Holmes gathered a large amount of disconnected information on the prevalence of intermittent fever in this region. In many cases, there can be no doubt that the disease concerned was malaria. In some accounts it is apparent that it was tertian malaria. Many of these outbreaks of intermittent fever were due to movements of population, concerned mainly with new construction, in particular dams, and the drainage of marshes.

*Commissioner, Massachusetts Department of Public Health; lecturer in public health practice, Harvard School of Public Health.

The first epidemic of malaria in Massachusetts took place at the close of the eighteenth century and existed in the western portions of both Massachusetts and Connecticut along the Housatonic River basin. The second epidemic appeared from 1828 to 1832 in Connecticut along the shore of Long Island Sound, and slowly moved in a northeasterly direction, eventually reaching western Massachusetts. No appreciable number of cases were reported in Massachusetts after 1836. The third epidemic began in New Haven about 1850 and remained within the vicinity of Long Island Sound for the ensuing fourteen years. In 1865, the disease began to spread northward, and it first appeared in Massachusetts in Springfield in 1870. During the ensuing nine years malaria spread in a northerly direction up the Housatonic and Connecticut rivers.

In 1880, Adams[2] made a survey of the malaria situation since 1836, by means of correspondence, personal observation and inquiry. By this means, the existence of malaria was ascertained in forty-eight cities and towns, and its absence in one hundred and sixty-three. There were no replies from one hundred and twenty-eight towns, but the author states that replies were received from almost every place of any size or importance.

In 1884, Chapin[3] wrote a paper entitled "The Origin and Progress of the Malarial Fever Now Prevalent in New England." He gave data on the occurrence of malaria in Massachusetts in 1881, 1882 and 1883. In 1881, malaria reappeared in the towns where it had appeared the previous year, with an increase in the number of cases and in mortality. Chapin remarks that the term "malaria" was beginning to replace the term "intermittent fever" in Massachusetts. In 1882, malarial diseases continued in the same towns, with an increase in deaths. In 1883, there was a general decrease in the number of cases, although nothing had been done in the way of sanitation to secure the result. Chapin judged