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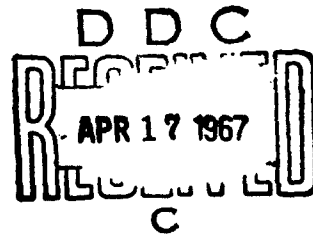
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IN RHEBUS MONKEYS
WITH ORGANIC PHOSPHATES

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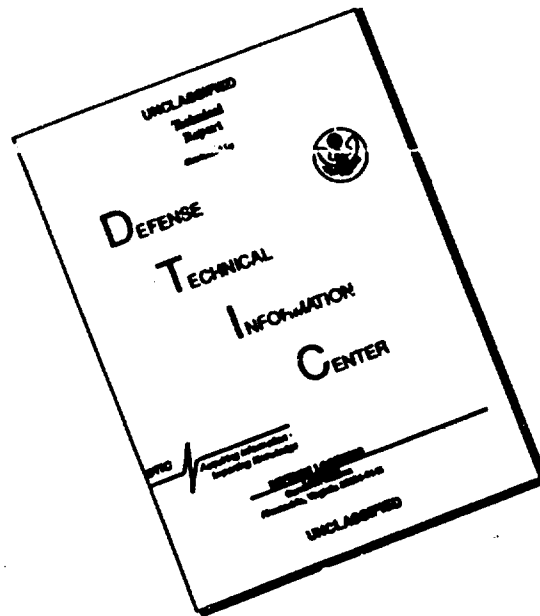
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MARCH 1967



DEPARTMENT OF THE ARMY
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TREATMENT OF PULMONARY ACARIASIS IN RHESUS MONKEYS
WITH ORGANIC PHOSPHATES

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Project 1C522301A059

March 1967

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences-National Research Council.

ABSTRACT

The use of rhesus monkeys for studies of pulmonary infections is complicated by a high incidence of scariasis due to Pneumonyssus simicola in the lungs of imported animals. Treatment of this infestation with the organic phosphate compound Ronnel significantly lowered the incidence of active lesions. Another organic phosphate, Trichlorfon, failed to show a therapeutic effect under the conditions of this study.

I. INTRODUCTION

The use of naturally bred imported rhesus monkeys (Macaca mulatta) in studies of pulmonary infections is complicated by the high incidence of Pneumonyssus simicola infestation of the lungs of these animals. Innes et al.,¹ Fairbrother and Hurst,² and Habermann and Williams³ have suggested that virtually 100% of imported rhesus monkeys have pulmonary acariasis, and observations during several hundred autopsies in this laboratory have revealed almost the same incidence. Although overt illness in the affected animals is not a problem, the presence of mites, frequently numerous in the individual monkey, may influence the study of experimental pulmonary disease in at least two ways: both gross and microscopic lesions may be confused with other chronic inflammatory lesions by the unsuspecting investigator, and the often extensive bronchiolectasia resulting from infestation may alter the response of the monkey to the induced infection.

In the only reported attempt to treat lung mite infestation,⁴ an organic arsenical, tryparsamide, had no significant effect. Because of the success of others in treating a number of animal parasite infestations with organic phosphates, including cattle grubs,⁵ horse bots,⁶ dog fleas,⁷ and nasal bots of sheep,⁸ two such compounds were assayed for their effectiveness in eliminating Pneumonyssus simicola from rhesus monkeys.

II. MATERIALS AND METHODS

Two independent trials were performed. In one, 12 monkeys of both sexes weighing 2.45 to 3.8 kg each and estimated to be 3 to 5 years old were treated with Ronnel* (0,0-dimethyl 0-2,4,5-trichlorophenyl phosphorothioate) given via stomach tube. After an initial dose of 110 mg per kg body weight, four of the 12 monkeys died between 1 hour and 4 days later. Prompt administration of 2 µg of atropine when symptoms were observed saved the remaining eight animals. Subsequent doses were 55 mg per kg body weight, every other day four times, then once weekly for 3 months, a total of 16 doses of 55 mg per kg body weight each. There were no further toxic effects during the period of treatment or the subsequent 3 months prior to sacrifice. For this trial, there were 11 monkeys caged and handled with the experimental group but given no Ronnel.

* Ectoral; Allied Laboratories, Inc., Pittman-Moore Co. Division, Indianapolis, Ind.

In a second trial 20 monkeys imported at a later date weighing 1.9 to 2.9 kg each and estimated to be 2 to 3 years old were treated with Trichlorfon* (0,0-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate) given intramuscularly. Doses were 25 mg per kg body weight twice a week for 4 weeks. A final treatment of 35 mg per kg body weight in the 5th week provoked signs of organic phosphate poisoning, including copious salivation, weakness of voluntary muscles, and diarrhea. Treatment with 2 µg of atropine intramuscularly completely counteracted the toxicity. The animals were sacrificed in four groups of five monkeys, the first at 2 weeks after treatment was stopped, and one of the other three groups at weekly intervals thereafter. Fourteen controls were housed with the experimental group throughout the 10 weeks and were used only for experimental surgery immediately prior to sacrifice.

In all cases the lungs were removed immediately after death and infused endotracheally with 10% neutral formalin. Each specimen was assigned a code number to preclude possible bias when counting and excising lesions. Following fixation, the lungs were sectioned through all lobes at 0.5-cm intervals and all suspicious lesions were removed for microscopic examination.

III. RESULTS

Gross observations were confirmed by histologic examination in all instances. There were no incidental pulmonary infections, malformations, or tumors to confuse the search for mite lesions. The histologic findings were similar to those of Innes et al.¹ Lesions were classified into active and inactive. The active category included all foci of bronchiolitis, whether or not mites were present in the section. The inflammatory reaction varied from a minimal infiltrate of lymphocytes and macrophages in a bronchiole that was normal in size or slightly dilated to a severe exudative reaction including polymorphonuclear leukocytes, eosinophils, lymphocytes, plasma cells, histiocytes, and multinucleated foreign-body giant cells. Associated with this exudative reaction was extension of inflammation into contiguous alveolar septa and alveoli. Intact mites were present in many lesions and partly necrotic mites in others, but no correlation could be made between presence or absence of a mite or its state of preservation and the degree of bronchiolitis. The most intense individual reactions were found in the lungs with the largest number of lesions of all kinds. The monkey with the heaviest infestation, including 10 viable mites, two lesions with fragmented mites, and 27 areas of bronchiolitis without

* Neguvon; Chemagro Corp., Hawthorn Road, Kansas City, Mo.

mites, had numerous eosinophils in the inflamed areas and displayed a unique eosinophil infiltrate of several branches of the pulmonary artery.

An inactive lesion was characterized by marked dilation of a bronchiole, with or without visible connection to a terminal bronchus of normal caliber. The wall consisted of a single layer of flattened epithelial cells supported by a thin fibrous stroma in which nodules of hypertrophied smooth muscle were present. In addition, there were numerous pigment-laden macrophages in the wall and frequent nodules of lymphocytes, some with germinal centers. Rarely, a fragment of mite, but never a complete form, was seen within the enlarged airspace, without detectable attachment to the wall or inflammatory reaction. The possibility of artifactual localization of such fragments due to sectioning appeared highly likely.

The number of active and inactive lesions in each trial is shown in Tables 1 and 2.

TABLE 1. NUMBER OF MITE LESIONS IN RONNEL TRIAL

	Active	Inactive	Total
Control (11 monkeys)	97 ^a /	18 ^b /	115
Treated (8 monkeys)	7 ^a /	62 ^b /	69

a,b. The probability of these differences between control and treated animals was <0.001 for both active and inactive lesions.

TABLE 2. NUMBER OF MITE LESIONS IN TRICHLORFON TRIAL

	Active	Inactive	Total
Control (14 monkeys)	28 ^a /	4	32 ^b /
Treated, early sacrifice (10 monkeys)	24	1	25
Treated, late sacrifice (10 monkeys)	11 ^a /	1	12 ^b /

a,b. No significant difference between control and treated animals.

IV. DISCUSSION

The effectiveness of Ronnel in converting active lesions to inactive ones is evident (Table 1). Treated monkeys had one-tenth the number of inflamed bronchioles per animal but had five times as many inactive lesions as a control group. These highly significant differences are based upon our interpretation of bronchiolectasia as a residual lesion of mite infestation, as opposed to an early stage in the process, as postulated by Innes et al.¹ The marked dilation of bronchioles was associated with considerable hypertrophy of smooth muscle, indicating that the process had been of some duration. Furthermore, if the fine to coarsely granular brown-black pigment found in the macrophages associated with such lesions does indeed derive from Pneumonyssus infestation, as indicated by Innes et al.,¹ the relative abundance of the pigment suggests long-standing infestation in these sites, rather than a recent onset.

Trichlorfon was tested because that compound can be given intramuscularly instead of by the inconvenient means of stomach tube, as required for Ronnel. Under the conditions of the study, there were no significant differences between the treated and control groups. However, in contrast to the Ronnel study, in which the monkeys were sacrificed for study 6 months after the onset of therapy, the longest follow-up time for Trichlorfon was 10 weeks. If the treated animals are subdivided into early (7 and 8 weeks) and late (9 and 10 weeks) sacrifice groups, there is a suggestion of a therapeutic effect in the late group. Perhaps a longer period of treatment and post-treatment wait would reveal equal effectiveness of this mode of therapy.

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The use of rhesus monkeys for studies of pulmonary infections is complicated by a high incidence of acariasis due to <u>Pneumonyssus simicola</u> in the lungs of imported animals. Treatment of this infestation with the organic phosphate compound Ronnel significantly lowered the incidence of active lesions. Another organic phosphate, Trichlorfon, failed to show a therapeutic effect under the conditions of this study.		
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