STUDIES OF THE PHARMACODYNAMICS AND MODES OF ACTION OF ANTHELMINTIC DRUGS

A THESIS PRESENTED IN PARTIAL FULFILMENT

OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

AT

MASSEY UNIVERSITY

U MIN SOE

1977

Abstract of a thesis presented in partial fulfilment
of the requirements for the Degree of Doctor of Philosophy

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The aim of this work is to extend existing knowledge both with respect to the mode of action of anthelmintics and the biochemical and physiological mechanisms which may be disrupted by drug action. The helminth species examined include nematodes, *Ascaris suum, Ascaridia galli* and *Trichuris ovis* and cestodes, *Moniezia, T. hydatigena, T. taeniaeformis* and *Echinoccocus granulosus;* the anthelmintics studied were methyridine, diethylcarbamazine, pyrantel, morantel, tetramisole, levamisole, dichlorvos, vincofos, cambendazole and mebendazole. The helminth characteristics selected for most intensive study are (a) the occurrence and properties of helminth cholinesterase and (b) the uptake of glucose. The breadth of the study was limited by the availability of fresh material and not all combinations of helminth and drug were investigated.

The histochemical localisation of cholinesterase activity in whole mounts and sections of tapeworms using thiocholine esters revealed a complex network of tegumental receptors feeding a nervous system with efferents to suckers, rostellum and hook muscles. It is suggested that tapeworms have reflex arcs involving these structures allowing them to maintain their position in the host intestine in spite of peristaltic action. These arcs are susceptible to anticholinesterase anthelmintics. Other cholinesterase activity is associated with the scolex, cirrus, genital pore and sometimes the tegument.

High cholinesterase specific activities against acetylthiocholine were measured in *Echinococcus* scoleces and tapeworms, but lower levels in nematodes. Differential centrifugation of homogenates was used to

study their occurrence in the tissue and facilitate further characterisation. However, the enzyme was widely distributed in these species although somewhat higher in the particulate fractions. Activity was increased little, if any, by attempts to solubilise it with the detergent, Triton X-100. Cholinesterase in some fractions particularly from *T. ovis*, had a high temperature optimum around 60°C, but never showed the phenomenon of autoinhibition by substrate at concentrations up to 10^{-2}M. Cholinesterase in species of worm with high levels of enzyme was more sensitive to eserine inhibition than those with lower levels.

In studies of glucose uptake from the medium by *Ascaris* and two tapeworms, it was confirmed that transport into *Ascaris* was strongly inhibited by certain benzimidazole anthelmintics. Transport into *Ascaris*, but not the cestodes, was also discovered to be sensitive to local anaesthetics such as procaine or lignocaine. Uptake into tapeworms was inhibited by the absence of sodium ions, phlorizin, iodoacetate and dinitrophenol. It was less inhibited by benzimidazoles and not at all by organophosphate anthelmintics, but was sensitive to phenolic drugs such as hexachlorophene and nitroxynil.

In the dog and sheep, a number of anthelmintic drugs administered intravenously showed predominantly nicotinic effects on blood pressure and respiration supporting the cholinergic action of these drugs. Although sheep red-cell cholinesterase is more sensitive to inhibition than that of all helminths tested, the oral route of administration of anthelmintics remains safe for the host and effective against intestinal parasitic worms.

ACKNOWLEDGMENT

I wish to express my gratitude to my chief supervisor Dr L.S. Forbes, who proposed the area of research covered in this thesis and for his suggestions and criticism and for the arrangements which were made for bringing this thesis to completion.

I am greatly indebted to my other supervisor, Dr. R.M. Greenway for his role in supervision, continued interest, and never-failing support and encouragement.

I have much pleasure in expressing my grateful thanks to Professor R.E. Munford, Head of the Department of Physiology and Anatomy, Massey University, for his computing and statistical analysis and the provision of laboratory facilities.

I wish to express my gratitude to Dr. D.D. Heath and staff at Wallaceville Animal Research Centre, Wellington, for supplying *T. ovis* cysts and for valuable suggestions.

I am indebted to Mrs Sharon Pickett for her technical assistance and typing of my manuscript and Mrs Fay Wicherts for her careful final typing. The enthusiastic technical assistance of Messrs R.N. Ward, B. O'Sullivan, and R. Telfer and our photographer, Mr T. Law are warmly appreciated.

Acknowledgements are due to the staff of the library, especially Miss E.M. Green, from the interloan section of the library at Massey University, for facilities in verifying the references from different libraries throughout New Zealand and overseas.

This investigation has been financially supported by the Burmese Government and the New Zealand Government under bilateral aid arrangement of Colombo Plan Scholarship and I am much indebted to both Governments.

Finally, I thank my mother Daw Kyaw Shin, who was deceased during the course of my studies, in Burma, for her upbringing and persistant encouragement and then my wife Kyi Kyi Nyunt and our son, Soe Wunna for their encouragement during our separation for the five years while I was engaged in this research in New Zealand.

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