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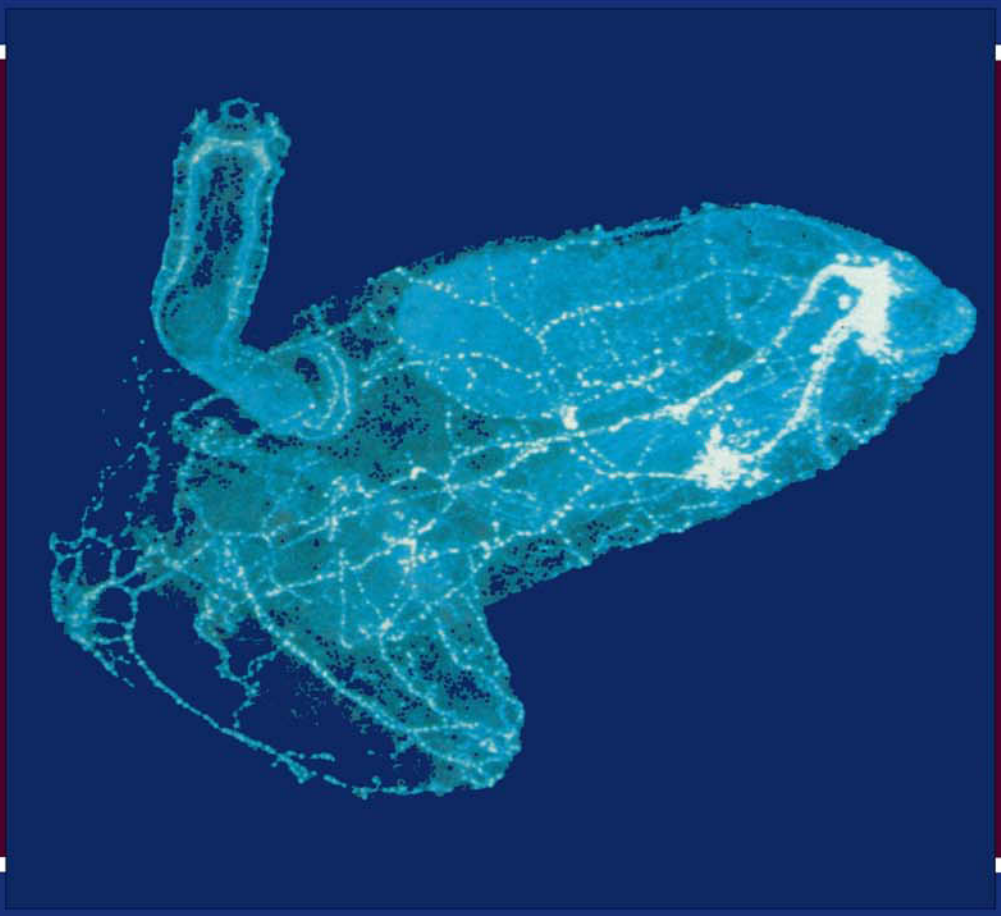
ADVANCES IN PARASITOLOGY



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Advances in
PARASITOLOGY

VOLUME 34

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PREFACE

As readers will already have noticed, *Advances in Parasitology* has had a "face lift" — a redesigned cover and some typographical changes which will, we hope, serve to make the series more attractive and a little easier to read. Coupled with these changes we intend to increase the frequency of publication from annual to roughly biannual. By so doing we hope to be able to give better coverage to the many recent and exciting advances brought about by the application of new approaches in molecular parasitology, immunology and epidemiology of parasitic diseases. In order to help with this new initiative the series has also acquired a third editor, Dr David Rollinson of the Department of Zoology at the Natural History Museum in London.

David Rollinson will be known to most, if not all, readers of *Advances in Parasitology* both as a highly respected parasitologist and as an editor of various books on the subject. We, the "old timers" (John Baker and Ralph Muller) warmly welcome him as a long-time friend and new colleague, and we feel sure that, with these changes, the series is established on a firm base for continued expansion into the 21st century.

The volume starts with two reviews concerned with molecular studies in relation to malaria, one concerned primarily with the insect vectors, the other with the parasites. Malaria is an increasingly important health problem in the world today. Effective control has been hampered by the development of insecticide resistance by the mosquito vectors and of drug resistance by the malaria parasite. Julian Crampton of the Liverpool School of Tropical Medicine reviews two important areas of research, both of which concern vector biology and malaria control. The first is the use of DNA probe technology to improve vector identification techniques. Many mosquito vectors are members of sibling species complexes which cannot be easily distinguished by morphological characters. There is a need to identify species in control programmes as the different species within a complex may exhibit differences in ecology, vectorial capacity and response to control measures, and new methods of DNA analysis can provide much needed alternatives for mosquito identification. The second area of research is quite novel and concerns the genetic manipulation of anophelines so as to disrupt the transmission cycle. The advent of

recombinant DNA technology and transgenic techniques now provides the means for the controlled genetic manipulation of vector genomes by the direct introduction of DNA into the insect germ line. A fascinating insight into the development of transgenic techniques for mosquitoes is provided, and the potential value and use of this remarkable technology are detailed.

Ribosomal RNA (rRNA) genes have been the subject of a number of detailed studies in recent years. Andrew Waters from the University of Leiden reviews the impact of such studies as they relate to the genus *Plasmodium* by considering three research areas: molecular biology, molecular phylogeny and diagnostics. This work clearly shows how unsuspected and interesting biological findings can emerge from detailed molecular research. *Plasmodium* species appear to have evolved an apparently unique response to the problem of living in mosquitoes and vertebrate hosts, and that is the switching ribosome. Two different types of rRNA gene, each containing unit specific sequence elements, are expressed in a stage specific manner. Nucleotide sequences of rRNA genes can be useful for constructing phylogenies. One of the intriguing findings, confirming earlier suspicions, is that the major human pathogen *P. falciparum* has a unique and distant relationship to other human and primate malarias. Sequence variation within the rRNA gene has also been exploited in polymerase chain reaction based diagnostic tests for the detection and identification of the malaria parasite — all this from one gene family!

A question that has taxed many parasitological minds is the extent and nature of molecular mimicry between parasite and host. Roger Hall from the University of York provides a refreshing and detailed overview of this topic and concludes that the existence of molecular mimicry as an adaptation of parasites to their hosts is an undoubted reality. He explores this fascinating area by first considering what is meant by molecular mimicry, how it might be studied, the consequences to host and parasite, and how widespread is it. Numerous examples of mimicry, some of them speculative, are considered and placed in four main classes: cytoadhesive proteins and their receptors; effectors of the immune system; hormones, serum proteins and their receptors; and cytoskeletal and muscle proteins. There are difficulties in recognizing and providing clear evidence for mimicry but in a few cases compelling explanations are available with some of the best examples being associated with microbial infections and autoimmune syndromes.

Traditionally, research on the chemotherapy and the immunology of parasitic infections has been carried out independently and the interaction and possible synergy between the effects of drugs and the immune response of the host has been little studied. Recently, enhancement or even dependence of effective chemotherapeutic action on host immune defences has been reported in various parasitic infections and Paul

Brindley from the Queensland Institute of Medical Research reviews new and important studies linking the efficacy of antischistosomal drugs to host immunological responses to schistosomes. He concludes that achieving a semi-immune state through repeated infection, or perhaps through vaccination, may allow lower curative doses of antischistosomal drugs to be used than in non-immune patients.

While neuroendocrine secretion in vertebrates has been recognized for several decades, many new regulatory peptides have been identified and isolated in the last twenty years. More recently, research on the origins of peptidergic signalling in invertebrate neurons has been made possible by advances in the techniques of radioimmunoassay and immunocytochemistry. David Halton and colleagues at the Queen's University in Belfast have been in the forefront of research in helminth neuropeptides, and here review this exciting and fruitful field of study. Many newer anthelmintics appear to act against parasite neuromusculature and it is likely that, when helminth regulatory peptides and their receptors have been fully characterized and a physiological function assigned to them, they will prove valuable as targets for drug action. The very elegant results which can be obtained demonstrating neuropeptide immunoreactivity in whole mounts of platyhelminths are illustrated by the cover photograph.

Finally, Chris Green (University of Bristol) has contributed an excellent review of the possibility of tsetse control by trapping. Although not a new topic, having been tried since at least 1910 with varying degrees of success (see Glasgow, J.P. and Potts, W.H., 1970, in "The African Trypanosomiases" edited by H.W. Mulligan; London: George Allen and Unwin, for a history of the early work), considerable advances have been made in recent years — largely as a result of greater understanding of what attracts *Glossina* to traps and the work of Einar Bursell, Chris Green and others on the use of olfactory attractants based originally on chemicals in the breath of cattle. With increasing fears about the development of insecticide resistance by insects, and the recognition of the adverse ecological effects of wide-scale application of insecticides, the "ecologically friendly" method of trapping has once again come to the fore amongst methods of controlling tsetse and, hence, both human and animal African trypanosomiasis.

JOHN BAKER
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1. GENERAL INTRODUCTION

Despite enormous efforts over many years, malaria is an increasingly important health problem in the world today. Some 500 million people are estimated to be affected each year, with approximately 3 million deaths (Sturchler, 1989). The incidence of this disease is increasing due largely to the development of insecticide resistance by the mosquito vectors and by the appearance of drug resistance in the malaria parasite. These factors are exacerbated by migration of increasing numbers of people from non-endemic areas to regions where malaria is prevalent.

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Research over the last century has increased our understanding of the complex relationship between insect vectors, the parasite causing the disease and the human host. One way of interrupting this cycle is to suppress the insect which acts as the vector and a number of techniques have been tried. These include chemical control through insecticides and larvicides, biological control through natural predators or toxins, such as that produced by *Bacillus thuringiensis*, environmental control through the removal of breeding sites and the raising of public awareness and genetic control through the mass release of sterile males. Another genetical approach, which may become a possibility through the advent of recombinant DNA technology, would be to compromise the vectorial capacity of the insect.

Despite the current trend towards integrated pest management, in which several approaches are used in combination to suppress insect populations, the main emphasis for mosquito control has been the elimination of breeding sites and the application of chemical agents. There are now considerable problems associated with the use of synthetic insecticides. The most important of these is the seemingly inevitable evolution of resistance and there are now populations which are multiply resistant to all four classes of insecticidal compound (organophosphates, organochlorines, carbamates and pyrethroids). Coupled with this is the high cost of developing and registering new insecticidal variants, increasing legislation over their use and growing environmental awareness over their toxic residues. Genetic control, through the mass release of sterile male mosquitoes, has also been attempted but with little success (Grover, 1985). This is now thought to be due to the poor competitive mating ability of treated males following chemical or radiological sterilization. Less traumatic sterilization treatments may increase the effectiveness of such a strategy, as demonstrated by the successful eradication of the screw-worm fly from the Southern USA (Krafsur *et al.*, 1987). However, such autocidal strategies of population control often prove prohibitively expensive since they involve the repeated mass release of treated males (McDonald *et al.*, 1977).

The problems associated with the widespread and continuing reliance on chemical insecticides has stimulated interest in alternative methods for malaria control. What is required is the development and evaluation of a new generation of methodologies which will have a profound and long-lasting effect on malaria transmission. Clearly, biotechnology and molecular biology can play a central role in the search for, and production of, such new tools. The development of potential antimalarial vaccines and biotechnologically produced larvicidal compounds are obvious examples of the power of the approach. Perhaps surprisingly, this technology has not been applied to the anopheline vectors of malaria until very recently.

Advances in the molecular analysis of vector–parasite relationships and vector molecular biology now make such an approach very attractive especially as past experience has shown that vector control is an effective way of disrupting malaria transmission.

Two applications of molecular biology will be considered in relation to vector biology and malaria control. The first is the utilization of DNA probe technology to improve vector identification techniques. The aim here is to enhance the efficiency of existing control measures by providing accurate data about vector populations. The second is a completely revolutionary approach to malaria control through genetic manipulation of anophelines so as to disrupt the parasite transmission cycle. There are many other areas where molecular biology will have a profound impact on our understanding of the insect vectors of malaria. However, these two examples serve to emphasize the power of this technology and they are reviewed below.

2. DNA PROBES FOR THE IDENTIFICATION OF MALARIA VECTORS

2.1. Current Methods for the Identification of Malaria Vectors

Many mosquito vectors are members of sibling species complexes. Sibling species are reproductively distinct but cannot be distinguished by morphological features alone and require alternative methods for identification. It is important to distinguish these species in control programmes as the different species within a complex may exhibit differences in ecology, vectorial capacity and response to control measures (White, 1982). There are a number of techniques available for the identification of vector specimens and these are discussed below.

The definitive method for species identification of mosquito malaria vectors such as the *Anopheles gambiae* complex, which includes the major vectors of malaria in Africa, is to perform crossing experiments of the offspring of the unknown specimen against laboratory colonies of known species (Davidson, 1964, 1966; Davidson and Hunt, 1973). Although this method has been of great value in the elucidation of species within a number of anopheline complexes, it is far too laborious and time consuming to use for routine identification of individuals.

Many external morphological characteristics of anopheline species have been examined in an attempt to identify species-specific features. In the *Anopheles gambiae* complex, some characteristics of *Anopheles melas* are fairly reliable for separation of this species from freshwater *Anopheles*