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Molecular biology and parasites

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Parasites, the central theme of the articles in this series, all have one thing in common, despite their biological differences – the uniformly negative connotation which they carry in our minds, as well as in our everyday language. Despised, feared, cursed, they are eternal threats to human well-being, destroyers of cultures and lethal enemies to development and prosperity in much of today's world. Consequently, all of the endeavours reviewed in this issue are directed towards the speedy elimination of the fiendish organisms from afflicted individuals and populations, as well as from their whole environment. Despite this emphasis of the current series of articles, let us not forget that this essentially negative view of parasites, however well-founded it may be because of the afflictions and the suffering which they bring upon us, is highly anthropocentric. In the wider context of biological evolution, parasites have always played an essential role as selective agents of evolution (Lively [14], Endler and Lyles [6], Pomiankowski [18], Hamilton and Zuk [10]), and therefore they are our partners, in a biological sense, as much as our foes. Also, much as we may deplore the ill-effects of parasitism on man and his domestic animals, parasitism is the way of life of the majority of organisms on our earth (Price [19]). Thus, if we are inclined to take a gloomy view of life we, the hosts, may consider ourselves as endangered minorities which survive on this planet merely to serve as substrates for the parasitic majority.

Be that as it may, the term 'parasite' itself has different connotations even in different biologists' minds. Traditionally, the term is applied to protozoa and multicellular eukaryotes. However, in a biological sense, many bacteria and all viruses have parasitic lifestyles, and the viruses in fact represent the ultimate parasites. This wider definition of parasitism has helped tremendously to overcome traditional barriers between the once widely separated fields of bacteriology, virology and parasitology. Nevertheless, the present collection of articles focuses on parasites in the more traditional sense (protozoa and worms), and even within this narrow framework it is necessarily incomplete. Its emphasis lies, in terms of organisms, on human disease agents, and in terms of technical approaches, on basic biology, diagnosis, epidemiology and vaccine development. Veterinary parasites are dealt with only briefly (Hide and Tait) and plant parasites (Camargo et al.[3]) are not considered at all. These omissions are due to space constraints only and not to an underestimation of the importance of these disease agents. They are at least as great a threat to human well-being as are the parasites that cause human disease, because they deprive man of essential resources such as food, energy, materials and tradeable goods. Another topic not addressed in the current issue is the important technical approach of drug development, but several reviews covering this topic have recently appeared (Fairlamb [7], Lacey [12], Gutteridge [9]).

Parasitology as a science has long been the exclusive domain of organismally oriented biologists, veterinarians and medical doctors. Within the last decade or so, some parts of this field have been rapidly and dramatically transformed (as have many other domains of biology and medicine) by the advent of molecular biology and concomitant developments in neighbouring sciences such as protein chemistry, computer science, immunology and instrumentation. The current collection of articles is intended to illustrate a few facets of these rapid and exciting developments, and to indicate where the usefulness of new technologies lies, not only for the laboratory scientist but also for the field epidemiologist and medical

worker at large. Besides the tremendous gains in insight into the basic cell biology of parasites, most notably the protozoal parasites, as exemplified by the article of Perry and Agabian, the development towards tools for medical applications has probably been fastest in the fields of diagnosis and epidemiology (Nantulya, Hide and Tait). Molecular and antibody probes are being developed with increasing speed, and these will allow an ever more refined detection and characterization of parasites both in the afflicted human or animal host and in vectors and intermediate hosts. Concomitantly with the development of parasite-specific reagents, great efforts were undertaken to improve detection technology and instrumentation. The initial detection methodology based on radioactive isotopes is rapidly being superseded by new generations of non-isotopic detection methods with increased speed and sensitivity (Diamandis[4], Leong et al.[13], Kricka and Thorpe[11], Messeri et al.[15]).
However, the brave new world unfolding rapidly in medical diagnostics also sharply calls to our attention an often-overlooked aspect of parasitology: the gap between the research laboratory and bedside application is wider by orders of magnitude than it is, say, in cancer diagnosis. Those afflicted most by parasites usually live far away from air-conditioned, computerized, automated and reliably electrified laboratories. Equipment which is regarded as standard in diagnostic laboratories in major clinical centres is not available, and often not practical, in such settings. Thus, much of the increased sensitivity, speed and simplicity brought about by new technologies is, alas, not readily applicable to parasitological field use. This is all the more deplorable as the speed of a diagnostic test is often more important when examining inhabitants of a remote area than when examining stationary patients in a big clinic, since patients in the former setting usually cannot be asked to come back in three days time for an evaluation of the test. Thus, despite tremendous developments in reagent specificity and sensitivity on the one hand, and in instrumentation and detection technology on the other, a wide gap still remains to be closed between the laboratory or clinical diagnostic environment and the diagnostic possibilities in the 'real' world of parasitology.
The issue is somewhat different in the field of vaccine development (Certa, Cryz, Taylor). Initially, high hopes were sparked by the advent of recombinant DNA technology for a speedy development of vaccines against numerous major diseases, but these hopes quickly faded and have been replaced by assessments varying from outright pessimism to cautious optimism paired with great patience. The limiting factor here is not so much technology, nor the lack of perseverance or brain power, nor even of money, but the dearth of our understanding of the inner workings of the immune system. In fact, the stimulation which parasite vaccine development received through the advent of recombinant DNA technology was instrumental in unravelling how little we realized how little was known about why any vaccine ever worked. Thus, parasite vaccine development, though not yet successful from an operational viewpoint, has already earned considerable merit as a major stimulant for current immunological research. The difficulties in developing recombinant vaccines are by no means peculiar to parasitic diseases, as is exemplified most vividly these days by the problems encountered in the campaign to develop a vaccine against the AIDS virus.
Clearly, parasitology in many of its domains has undergone an unprecedented development over the last decade and has developed, for better or worse, into a boom area of the biological sciences. Much credit for this development certainly goes to TDR (Special Programme for Research and Training in Tropical Diseases) and related programmes of the WHO, the UNDP and the World Bank, and to similar major programmes sponsored by private foundations. In conjunction, these programmes have been spectacularly successful in initiating, with the prestige of their donor organizations and (relatively) little seed money, an unprecedented influx of interest and talent into the field. The research activation sparked by these programmes has subsequently attracted ample outside support from many sources not previously involved in funding parasitological research.
This course of events has succeeded in developing parasitology from a largely neglected sideshow of basic biomedical research into a major field of action and scientific progress. This has led to dramatic advances in the molecular analysis of parasite structure and function and in our understanding of parasite biology on the biochemical and molecular level. Furthermore, a development not unfamiliar to the biological sciences has taken place; progress in parasite research not only advanced our knowledge and understanding of parasite biology per se, but also demonstrated very soon that parasites, quite apart from their medical significance, can often be highly attractive model systems for basic cell biology. This is exemplified by the discovery of RNA editing and trans-splicing in trypanosomes (Perry and Agabian, this issue; Benne[1], Blum et al.[2], Weiner and Maizels[20]), the identification of glycolipid anchors as a widespread feature of protein/membrane interaction (Ferguson et al.[8]), or the molecular mechanisms by which drug resistance is acquired (Peterson et al.[17], Ellenberger and Beverley[5], Peters[16]). This newly gained 'standing' of parasitology as a respected branch of molecular biology has led to numerous new interactions and to the scientific cross-fertilizations which are so essential for any field to prosper. On the other hand, improved coordination and cooperation between laboratory and field have helped to make the interface between these two worlds considerably smoother, and to reduce the width of the gap between them.
Incidentally, 'going molecular' relatively late may prove in the end to have been a boon for parasitology. The increased awareness of parasites as fascinating organisms

for scientific research came at a time when many fields of science were undergoing rapid development and people were looking for novel applications and model systems. Parasitology was recognized as an area of potential interest by many groups simultaneously, and thus underwent an amazingly rapid development when compared to many other fields. A helping hand for this development may also have come from the spectrum of diseases associated with the AIDS epidemic. While parasitic diseases were clearly not uppermost in the hearts and minds of most industrialized countries and their funding agencies, the resurgence of opportunistic parasite infections in AIDS patients may have sharpened public awareness of the significance of parasitic diseases.

This latter point is a reminder that containment, prevention and treatment of parasitic diseases also face obstacles even more difficult than those due simply to the molecules involved and their mutual interactions. To judge by our experience of the past, basic research can be trusted to tell us much about the molecular mechanisms underlying parasitic disease. Building on this scientific basis, 'high-tech' solutions to many problems of disease prevention and therapy are likely to be developed. Eventually, many of these solutions will eventually be converted to techniques which are applicable in the field, and guarded optimism is certainly justified. However, the difficulty of this last step is often drastically underestimated. While pharmaceutical companies all over the world strive to find formulations which allow the most convenient and effective application of their drugs or vaccines, many of the forms of application suitable for patients in industrialized countries may not be practicable for treatment and prevention of parasitic diseases. Patients may not be available three times at monthly intervals to be given injections, medicines to be taken twice a day after meals for four weeks are useless, diagnostic tests which take days to perform and thus necessitate the return of the patient for subsequent treatment are of very limited value, and the necessary infrastructure of transportation, cool-chains, electricity and the like may not be available or not reliably so.

Thus, in addition to the development of new curative and preventive treatments using the latest molecular and biochemical wizardry, problems of logistics and application will have to be solved which are unique to parasitic diseases, and for which there are no well-established precedents from the development of antacids or anti-hypertensive drugs. Such developments will clearly be costly, both in terms of money and of trained brain and manual power. Both resources are limited – disastrously so in the countries most afflicted by parasitic disease, but also, if for different reasons, in all other countries as well. It is most unfortunate that, in the long run, these obstacles may be more difficult to overcome than the remaining scientific hurdles. The guarded optimism which is certainly appropriate when considering the current progress towards diagnostics, vaccination and drug development for parasitic diseases is superseded by pessimism in view of the fact that today even vaccines which are readily available, proven and working (such as those against diphtheria or tetanus) cannot be applied to large segments of our world's population for logistic and financial reasons.

The economics of the development and implementation of diagnostic kits or vaccines are facts of life which are easily overlooked when concentrating on the microlitre world limited by Eppendorf tubes or microtitre wells. It is certainly a good thing to develop a workable diagnostic test in the laboratory. But which enthusiastic scientist, buoyed up by the successful experiment documented by black spots on a film, or a positive readout on whatever fancy equipment used to develop this great new diagnostic test, would ever go through the drudgery of adding up just how much was spent to get that far? (The grant size is an insufficient approximation.) And this is just the beginning. Our successful scientist will need a lot more than what has already been spent to validate the test under field conditions, using real specimens from real patients, cows, flies, snails or whatever, and having to adapt the test and its reagents to a world without deep-freezers, image processors and thermocyclers.

Let us assume that our scientist still finds sufficient funding and an incredible streak of good luck which allows a successful completion of this phase; even then, the test reagents still have to be standardized and mass-produced, which in itself is a major and cost-intensive undertaking. The course of events is similar for vaccines; just add a few steps for safety and efficiency testing, and mark up the cost factor for each step by a few orders of magnitude. Were our scientist not a scientist but the accounting officer of a commercial enterprise, the undertaking would have been abandoned long before, because of the simple question: 'Will those needing these tests or shots ever be able to pay for all of that?'

While ways and means are actively being sought by all involved to overcome this sticky point in each and every development towards diagnosis and treatment, another finance-related aspect should also not be neglected as a result of all the excitement and expectations generated by recombinant DNA technology. It is a trivial but often forgotten fact that for many parasitic diseases, the most cost-effective approach by a wide margin is clearly prevention. There is nothing new, nor spectacular, nor high-tech and fancy in this approach, just a list of those old and proven measures such as improved housing to eliminate the habitats of house-dwelling disease vectors, sanitation to control the spread of the myriads of intestinal parasites, improving the quality of water and a careful management of this water supply in order to contain the waterborne parasite vectors and their intermediate hosts, and numerous other measures of this humble but effective kind. This again is nothing peculiar to the epidemiology of parasitic diseases or to Third World countries – the epidemiological history of the industrialized world is ample demonstration that sanitation and the establishment of a reliable, good-quality water supply were the decisive factors in eliminating many of the major infectious diseases which were no less threatening to Europe a century or two ago than parasitic diseases still are to many parts of our world today.

Within the multifacetted context of parasitic disease, molecular biology and its scientific ramifications have contributed significantly, and will continue to do so, both to our understanding of basic mechanisms of parasite biology and its interaction with that of hosts and vectors, and to the development of novel and more efficient diagnostic and, it is to be hoped, therapeutic tools. Nevertheless, it would certainly be unwise to expect a solution for every problem to be found in the pills and potions eventually developed by recombinant DNA technology, and it will be helpful for all involved to keep the perspective right by remembering the profound insight of the great parasitologist William Trager: 'Good plumbing has done more for good health than has good medicine'.

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Unsolved and controversial issues in human nutrition

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Unsolved and controversial issues in human nutrition. Introduction

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There are particular areas in medical research where our knowledge is growing rapidly and where certain concepts are constantly being challenged and questioned. Research in human nutrition is a potential candidate for controversy owing to a number of limitations related to experimental, ethical, statistical, environmental and genetic considerations. Indeed, in the field of nutrition and health pseudo-scientific beliefs, speculations based on emotional discussion rather than experimental evidence, and dogmatic positions (i.e. food faddism and quackery) appear still to be widely prevalent. For example, the belief that megadoses of certain nutrients (in particular a number of vitamins and several trace elements) have unique preventive or curative properties in man may be more widely disseminated than currently thought.

The Swiss Nutrition Society organizes a symposium every 3 years dealing with a topic where new information has been generated and updated information is required.