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Malaria: Drugs, Disease and Post-genomic Biology

With 40 Figures and 15 Tables

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DS dedicates this volume to his parents, brothers and Lois, Luke, Benjamin and Ronan and SK to his parents, Ash, Niraj, Arti, Anand, Yasmin, and last, littlest but not least to Karim.

Preface

There are more than 120 species of *Plasmodium*, but only five naturally infect humans. *P. malariae*, *P. ovale*, *P. vivax* and occasionally *P. knowlesi* cause cyclical fevers, anemia and splenomegaly the classic triad associated with the clinical syndrome of malaria. The fifth organism, *P. falciparum* is lethal because it can achieve high parasitemias and additionally bind to endothelial cells and disrupt organ function. *P. falciparum* was the first species for which continuous *in vitro* cultivation was developed by William Trager and James Jensen in 1976. This milestone in malariology launched an intense study of biochemistry of parasites, identification of vaccine candidates and drug targets and most recently completion of the *P. falciparum* genome. However, despite rapid increases in knowledge, malaria continues to kill more than a million people each year and to cause symptomatic disease in a further 300 million individuals.

Specific antimicrobial treatment for malaria was available hundreds of years before Alphonse Laveran first described the etiologic agent in 1880. P.G. Bray et al. begin this volume with an account of the history and biologic chemistry of the widely used and highly effective quinoline and artemisinin drug classes. *P. falciparum* has evolved resistance to most classes of antimalarials, which worsens clinical outcomes particularly in the most vulnerable populations of women and children. A.-C. Uhlemann and S. Krishna describe the mechanisms of drug resistance with special attention to the hotbed of drug resistance in southeast Asia, while C.V. Plowe outlines strategies for monitoring and deterrence of drug resistance, chiefly in Africa.

There can be almost a trillion *P. falciparum* parasites in an infected individual equivalent to tens of milligrams of protein, distinguishing malaria from bacterial infections where millions of bacteria produce nanograms of protein. M.P. Grobusch and P.G. Kremsner describe the diversity of syndromes seen in uncomplicated malaria, while T. Planche et al. describe the metabolic consequences of severe malaria. D.J. Roberts et al. highlight the pathogenesis of severe anemia. *P. falciparum* exports adhesive ligands to the exterior of the host erythocyte, a property associated with organ dysfunction affecting lungs, kidneys, liver and brain. P.E. Duffy and M. Fried explain how these mechanisms affect *P. falciparum* sequestration resulting in placental malaria.

The several-fold rise in *P. falciparum* numbers every 2 days in unrestricted infections requires many unique metabolic adaptations to the hemoglobin

rich erythrocyte. S.S. Oh and A.H. Chisti highlight host invasion receptors and parasite ligands necessary for merozoite invasion of the erythrocyte. Subsisting almost entirely on glycolysis, the intraerythrocytic parasite still requires function from its single acristate mitochondrion. In close apposition to the mitochondrion is the unique plant-derived plastid organelle. A.B. Vaidya and M.W. Mather and S. Sato and R.J.M. Wilson describe the genomic framework for understanding plastid and mitochondrial physiology. This has already been exploited by identifying new drug targets and additional unique vulnerable pathways are also being studied as future targets. D.E. Goldberg catalogues the specific, efficient hemoglobin proteases that provide amino acids and space for the development of the *Plasmodium* parasite. P.F. Scholl et al. detail the intersection of host and parasite iron pathways that, for the parasite, center on heme crystal formation called hemozoin. K. Kirk et al. review a "permeomic" description of membrane transport proteins critical to nutrient support of development, and that also affect antimalarial drug action and resistance.

During the rapid asexual haploid replication that causes symptoms in patients, less than a thousandth of the total number of parasites differentiate into the sexual gametocytes, which in turn are taken up in the bloodmeal of the female Anopheles mosquito. From a few hundred gametes in a bloodmeal, a handful of zygotes mature to ookinetes. J.M. Vinetz details ookinete biology as it traverses from the gut to the outside of the stomach to form the oocyst. The oocysts, in a few days time release thousands of sporozoites that migrate to the salivary glands in preparation for inoculation. K.D. Vernick et al. explain the molecular genetics of mosquito-specific resistance to *Plasmodium* survival in the vector. Finally a few hundred infectious sporozoites are injected into the human bloodstream where only a couple will invade liver cells within 90 min. After 7–10 days the asymptomatic intrahepatic *Plasmodium* has rapidly multiplied to several thousand schizonts, and soon releases infectious merozoites to begin a cycle that has persisted in humans for millennia. P.L. Blair and D.J. Carruci in a *tour de force* of mass spectrometry credential the existence of protein products in the sporozoite and hepatic stages, which have proved very difficult to cultivate.

There is much that is new, exciting and potentially of clinical relevance since malaria parasites were first cultured. Some of these advances have been superbly captured in the chapters presented in this volume. The editors particularly wish to thank Mrs. Rina Patel, whose assistance in preparing this volume has been invaluable, and Gary Knight, whose photos on malaria are well known, for publishing one here.

June 2005 David Sullivan and Sanjeev Krishna

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(Addresses stated at the beginning of respective chapters)

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Drugs and Drug Resistance