Magic Bullets To Conquer Malaria
Magic Bullets To Conquer Malaria
From Quinine to Qinghaosu

Irwin W. Sherman

Department of Biology
University of California
Riverside, California

Department of Cell Biology
The Scripps Research Institute
La Jolla, California
For Vilia

Memories of our life together will never fade
# Contents

Preface          ix

1 From Breathing Bad Air to Biting Beasts     1
2 Myth to Medicine: Quinine              23
3 Synthetic Dyes to Drugs: Atabrine and Chloroquine    52
4 Antimicrobials to Antimalarials: Prontosil, Pyrimethamine, Proguanil, and Atovaquone  81
5 To Destroy Liver Stages: Primaquine and Tafenoquine  120
6 Quinine to Mefloquine               137
7 Reversal of Fortune            150
8 Sweet Wormwood of Success: Qinghaosu    168
9 Antibiotics and the Apicoplast       182
10 A Possible Dream: Control by Blocking Transmission  204
11 The Dream of Eradication            240
12 A Reasonable Dream                245

References    257

Index          277
Preface

This book chronicles the search for and use of medicines to conquer malaria, one of the world’s most devastating and debilitating infectious diseases. Currently there are about half a billion cases of malaria worldwide. The deadly malaria parasite, *Plasmodium falciparum*, on its own kills a million people per year, mostly children under the age of 5 years. Malaria imposes a significant economic toll. It is estimated that African nations alone lose $12 billion in gross domestic product each year due to malaria, which slows their annual economic growth by more than 1%. In some countries, malaria is responsible for up to 40% of the public health expenditures and malaria treatments can consume a third or more of the income of poor households. Faced with such enormous public health and economic problems, in 2008 the Roll Back Malaria (RBM) partnership launched the Global Action Plan aimed at reducing malaria mortality and morbidity by half from the rates in 2000, reducing the number of deaths to zero by 2015, and moving the goal of the program from control to eradication. If the plan is successful, 4.2 million lives could be saved by 2015.

The RBM partnership, started in 1998 as an alliance of four United Nations agencies, has now grown to become a coalition of more than 500 partners. The coalition’s ambitious assault, coordinated by RBM and referred to in the press as “the billion-dollar malaria moment” because of the substantial increases in resources from the Bill and Melinda Gates Foundation; the Global Fund to Fight AIDS, Tuberculosis and Malaria; the World Bank; and the President’s Malaria Initiative, echoes in some measure a past campaign at eradication.
Indeed, as far back as 1955 the World Health Assembly endorsed a policy of global eradication of malaria. This international campaign was fueled by the effectiveness of the residual insecticide DDT (dichlorodiphenyltrichloroethane) to destroy malaria-transmitting mosquitoes as well as the availability of a powerful and inexpensive medicine (chloroquine). In addition, there was the optimistic prospect of interrupting malaria transmission based on the mathematical modeling of malaria epidemiology carried out by Sir Ronald Ross and George MacDonald. With such an armory and strategy, the World Health Organization (WHO) expected that there would be a quick fix.

This was the landscape of malaria research in 1957, the year of my entry into the field, a time that could not have been less encouraging to a newly minted Ph.D. in biochemical parasitology, since if eradication succeeded, it surely would make any need for my efforts superfluous. However, less than a decade after the WHO announcement, all hopes for eradication were dashed and the Global Malaria Eradication Program was in tatters. By 1962, there were already increasing numbers of reports that chloroquine was not the infallible drug the “eradicators” had believed it to be, mosquitoes were no longer susceptible to the killing power of DDT, and there was a new and devastating war in Southeast Asia, with more and more civilians and soldiers succumbing to malaria. It became apparent that malaria would once again rank as a top medical priority for the U.S. Department of Defense. Thus, in 1963, the Malaria Research and Development Program of the U.S. Army was established, with an initial major objective of treating chloroquine-resistant malaria. In late August 1963, an international workshop entitled “Cultivation of Plasmodia and the Immunology of Malaria,” organized by Elvio Sadun of the Walter Reed Army Institute of Research (WRAIR), was convened in Washington, D.C. Its goals were to summarize the available information, to delineate some of the most urgent problems, to explore new approaches to current problems, and to devise methods to grow malaria parasites in the laboratory. On the basis of the discussions at the conference, it was clear that although a vaccine against malaria was a justifiable goal, its development would be long-term. The immediate problem, however, was to find new drugs to protect and treat people exposed to the increasing numbers of malaria parasite strains that no longer responded to chloroquine. Sadun organized a program at WRAIR to conduct investigations in malaria, to attract highly capable scientists from various disciplines to carry out malaria research, and to produce a continuing flow of highly trained people able to contribute to the management and control of this disease. In addition, a
new Commission on Malaria was established by the Armed Forces Epidemiological Board in October 1964, and the director of WRAIR, Colonel William Tigertt, began the largest antimalarial drug screening program ever undertaken—one that continues to this day.

A Second International Panel Workshop was held at WRAIR in 1966 to discuss the biology of malaria. At this workshop, to which I was invited, attention was given to the biochemistry of the parasite, the possible use of antibacterials for the prevention or treatment of chloroquine-resistant malaria, and in particular the potential value of combining sulfonamides with pyrimethamine (Daraprim) for therapy. Two workers at the National Institutes of Health had observed that pyrimethamine killed the malaria parasite by preventing its reproduction; however, they left unanswered the question of precisely why the killing took place. That is where I, as a budding biochemist, entered the picture. In 1968, my laboratory (then consisting of a graduate student, Charles Walsh, and myself!), supported by a grant from the U.S. Army, was looking into the simple building blocks needed to manufacture the parasite’s DNA. Much to our surprise, we found that the malarial parasites contained all the enzymes necessary to synthesize pyrimidines from scratch but the enzymes for purine synthesis were absent. This discovery led to an understanding of how pyrimethamine worked: it acted on a specific enzyme in the pyrimidine pathway, and when this enzyme was “knocked out” by the drug, the parasites were unable to make DNA and could not reproduce. As a result of this unintended foray into malaria therapy, I joined an increasing number of researchers who found themselves interested in how and why antimalarial medicines worked. Indeed, for the next three decades, a considerable portion of my research effort was dedicated to discovering the biochemical Achilles’ heels of the parasite.

By 1972, when the Global Malaria Eradication Program was formally declared dead, new approaches toward control of malaria were being considered by public health agencies. In 1975, a group of donor nations provided money to establish the United Nations Development Programme/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) to forge weapons for use in the fight against the six major tropical diseases, namely, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis, leprosy, and malaria. This ambitious program was designed to encourage research into the development of new drugs and vaccines, to establish research centers in countries where the diseases were endemic, to carry out field research and field trials, and to study the socioeconomic problems hindering progress. When the first TDR Task Force
on the Chemotherapy of Malaria (CHEMAL) met in Geneva in 1976, the participants felt that there was a need to investigate the modes of action of existing drugs, including the biochemistry of the parasites and the ways in which drug resistance develops; to find experimental models; to uncover better ways to deploy existing drugs; to seek ways of preventing the development of drug resistance; and to explore new ways to develop effective and potent antimalarials. The work of CHEMAL would take place through a Steering Committee. I was invited to become a member of the CHEMAL Steering Committee and served on that committee from 1978 to 1986. Close links were established between WRAIR, CHEMAL, and the pharmaceutical industry, and the first product of the cooperative venture was mefloquine. Later, CHEMAL would be involved in development of the novel Chinese antimalarial qinghaosu.

In 1999 the Medicines for Malaria Venture (MMV), based in Geneva, was founded. It is a nonprofit organization focused on the discovery, development, and delivery of new medicines for the treatment and prevention of malaria. It receives support from public and philanthropic funds and partners with academia, the pharmaceutical industry, and countries where malaria is endemic to realize its goals of finding and deploying “magic bullets” to cure malaria.

Recently four interventions, sleeping under insecticide-treated bed nets, spraying houses with insecticide, preventive drug treatments for pregnant women, and curing the sick with effective medicines, have promoted renewed interest and commitment to eliminating malaria. Although these are keystones in the RBM program, effective medicines offer the only practical solution to significantly reduce the spread of the disease and case management remains a cornerstone of malaria control strategies. At this time, as we contemplate a renewed attack to rid ourselves of the burden malaria places on half of the world’s population, it seems appropriate to examine how the drugs in the armory came into being, how they have been used and abused, the mechanisms of drug action, and the ways in which the parasite is able to fight back either by multiplying or surviving in the presence of a concentration of a drug that normally is able to destroy or prevent the parasite from reproducing. I hope that through an examination of drug treatments past and present, the problem of drug resistance, the greatest impediment to eradication, will be better understood so that its effects can be thwarted, and we will come to better appreciate the medicines (and other tactics) needed to head off the impending catastrophe that now looms large in the world.
A Note to the Reader

Interspersed in the text, chemical formulas and structures appear. These should not be a deterrent should your knowledge of chemistry be limited. Rather, the formulas and structures are provided so that those with the appropriate background as well as some without it may better appreciate the relationship between chemical structure and function. Even without reference to these chemical formulas and structures, the text itself should be entirely comprehensible to all.

Portions of chapters 1, 2, and 10 have been published previously in my books *The Power of Plagues* (ASM Press, 2006) and *The Elusive Malaria Vaccine. Miracle or Mirage?* (ASM Press, 2009).

Irwin W. Sherman
The Scripps Research Institute
La Jolla, California
Index

A
Abbott Laboratories, 142
Academy of Military Medical Sciences, China, 250–251
Acetyl coenzyme A, in fatty acid synthesis, 198
Acid-fast stains, 60
Acridine, 67–76
Acupuncture, for malaria, 169
AE, see Arteether (AE)
Aedes mosquitoes, 12, 41
Affordable Medicines Facility for Malaria, 240
Africa
bed nets for, 238–239
cinchona tree plantation in, 160–161
control efforts in, 212
endemicity in, 227
exploration and exploitation of, 31–39
vaccine trials in, 233–235
African Association, 33
Agfa (Aktiengesellschaft für Anilinfrabrikation), 83
Agriculture
mosquito population and, 43–46
organic chemistry effects on, 53, 55
AL (artelinic acid), 175
Albert (prince of England), 55
Albert I (king of Belgium), 160–161
Allyltoluidine, 57–58
Alonso, Pedro, 233
Alving, Alf S., 121, 128, 132
AM, see Artemether (AM)
American Cyanamid Company, 188, 194
American Revolution, 43–48
American South, eradication programs in, 206
Amino group, on aniline, 55
9-Aminoacridine, 68
4-Aminobenzenesulfonamide, 88
4-Aminoquinolines, 126
8-Aminoquinolines, 133–134
Amodiaquine, 178, 246, 253
Amyris Biotechnologies, 180
Anand, Nitya, 146
Anemia, hemolytic, primaquine-induced, 129, 132
Aniline
in coal tar fraction, 54–55
oxidation of, 57–58
structure of, 57
Aniline purple, 58
Animal studies, 13–14, see also Bird malaria; Mouse malaria; Primate malaria
Anopheles, 12, 16, 18
  in American South, 42–46
  in Panama, 42
Anopheles dureni, 221
Anopheles freeborni, 43
Anopheles quadrimaculatus, 43
Antibiotics, 251–252, see also specific antibiotics
targeting apicoplasts, 187–203
Antibodies
to gametes, 215–216
from host, 213–214
monoclonal, for vaccines, 216–217
Antifolates, 249, see also specific drugs
  resistance to, 161–163
  sulfonamides as, 92–93
Apicoplasts, as antibiotic targets, 187–203
Aralen, 126, see also Chloroquine
Arsenicals, 62
Arseno-phenylglycine, 62–63
Artecefin, 175
Arteether (AE), 252
  pharmacokinetics of, 176
  structure of, 173
  toxicity of, 173–174
Artekin, 253
Artelinic acid (AL), 175
Artemether (AM), 252
  development of, 174
  formulations for, 174
  pharmacokinetics of, 176
  structure of, 173
  toxicity of, 173
Artemisia annua
  acreage of, 179–181
  active ingredient of, see Artemisinin (qinghaosu)
  ancient use of, 171
  growing in North America, 173–174
  hybrids of, 181
  yield of, 178–179
Artemisinic acid, structure of, 175
Artemisinin (qinghaosu), 146, 168–181, 252
  in combination therapy, 177–178, 243–244, 250, 253
  derivatives of, 173–176
  development of, 168–171
  discovery of, 171
  dosage for, 178
  formulations of, 174
  isolation of, 171–173
  mechanisms of action of, 176
  pharmacokinetics of, 176
  price of, 179
  resistance to, 177–178
  structure of, 171–172, 175
  synthesis of, 178–181
Artemisinin Project, 180
Artemotil, see Artesunate (AS, artemotil)
Artequin, 178
Artesunate (AS, artemotil), 117, 252, 253
  formulations for, 174–176
  patents for, 175
  structure of, 175
AS, see Artesunate (AS, artemotil)
Association for Promoting the Discovery of the Interior Parts of Africa, 33
Atabrine, 67–76
  development of, 67–68
  dosage for, 71–73
  Fairley work with, 73–76
  introduction to United States, 69–70
  marketing of, 104
  Shannon work with, 72–73
  structure of, 69
  in World War II, 70–73, 126
Atlantic slave trade, 32–35
Atovaquone, 107, 252
  development of, 108–116
  efficacy of, 116
  mechanism of action of, 117–119
  structure of, 115
Atoxyl, 62
Aureomycin, 194–196
Avery, Oswald, 152–153, 182, 191
Azithromycin, 194, 202–203, 252
Azo dyes, 82–89
Azure B stain, 61–62

B
Bacillus brevis, 191
Bacillus malariae, 4, 5
Bacillus megaterium, 180
Bacteriophages, in DNA technology, 156

closo\-chlosoquine production at, 77
dye products of, 122–125
Beaudoin, Richard, 222–223
Bed nets, 206, 238–239, 243–244
Beesley, J. E., 110–111
Belgian Congo, cinchona tree
plantation in, 160–161
Benda, Ludwig, 62
Benflumetol, 178, 250–251
Benzene
aniline synthesis from, 54–55
as coal tar product, 53–55
Kekulé dream about, 54
structure of, 54
Benzylpenicillin, 190

Bignami, Amico, 8, 15, 17, 159
Biguanide, 106–107
Bill and Melinda Gates Foundation
artemisinin program of, 180
Ballou at, 237
eradication challenge of, 240–244
vaccine grant from, 233–234,
237–238

Bird malaria
antibiotics for, 195–196
Atabrine for, 77–78
pamaquine for, 125
parasites in, 13–14
research on, 221
sulfonamides for, 91–92

“Bitter lemon beverage, 51
“Bitter solution” (quinine), 26
Blackwater fever, 51, 247
Blood, parasite discovery in, 4–9
Blount, Brigadier General Robert, 137
Board for the Coordination of
Malaria Studies, 76, 112
Boehringer-Mannheim, 160–161
Bonaparte, Napoleon, 56
Bonification, of Italy, 48–50
Book of Epidemics (Hippocrates), 2
Brady, Robert, 25
Brazil, mosquito control in, 209–210
Breeding sites, for mosquitoes,
see Wetlands and mosquito
breeding sites
Brodie, Bernard, 72
Brossi, Arnold, 146, 170–171
Brumpt, Emile, 90
Buparvaquone, 116–117
Burroughs Wellcome Company, 94–96, 116, 118, 142
Burton, Richard, 37
BW58C (3-hydroxy-1,4-
naphthoquinone), 115
BW556C (naphthoquinone), 115, see also Atovaquone
C
Cairns Hospital, Australia, Atabrine studies at, 74–76
California gold rush, Panama Canal and, 40
California Institute for Quantitative Biomedical Research, 180
Canal Zone, 41
Canaries, quinine for, 64
Canfield, Craig J., 107–108, 139, 142, 146
Cão, Diogo, 34
Carroll, Lewis, 245
Carter, Henry Vandyke, 8
Carter, Richard, 215–219
Cassella Dyeworks, Germany, 62
Caventou, Joseph, 27
Celli, Angelo, 6–7, 48–49
Center for Traditional Medicine, Beijing, 169
Ceylon, malaria epidemic in (1934–1935), 207
Chain, Ernst, 189–191
Chargaff, Erwin, 153
Chargaff’s rule, 182
Charles II (king of England), 25–26
Chaucer, Geoffrey, 3
Chemotherapy, beginning of, 60
Chemotherapy and Drug Resistance in Malaria (Peters), 146
Chemotherapy of Malaria Steering Committee
artemisinin project of, 168–170
mefloquine program of, 140–141, 145–146
parasite DNA studies of, 184
Chicken malaria
1-p-chloroanilinopyrimidine for, 105
sulfanilamide for, 90
vaccines for, 215–221
Children, vaccine trials in, 233–234
Chin, William, 168
China
lumefantrine development in, 250–251
piperazine production in, 250
pyronaridine synthesis in, 251
qinghaosu from, 168–181, 252
Chinchón, Count and Countess of, 23–24, 27
Chinese National Malaria Control Program, 250
Chinoplast, 125
Chloramphenicol, 193–194, 202
Chlorcycloguanil, resistance to, 162
Chloroacridine, 68
1-p-Chloroanilinopyrimidine, 105
Chloroquine, 76–80, 247–248
discovery of, 76–78
in Global Malaria Eradication Program, 150–151
malaria pigment and, 164–166
primaquine with, 131–132
prophylactic, 78–80
resistance to, 164–166, 248–249
structure of, 78
toxicity of, 78–79
Cholesterol, for fatty acid synthesis, 198
Chorismate, synthesis of, 198–199
Chou, A. C., 165
Christophers, Sir Rickard, 205
Chromosomes, of parasites, 155, 158
Chrysiodine, 85–86
Churchill, Winston, 88–89
Cinchona bark
adulteration of, 26
harvesting of, 27
price of, 26
use in Peru, 23–24
Cinchna calisaya, 28, 30
Cinchna ledgeriana, 30
Cinchna officinalis, 27
Cinchna succirubra, 28, 30
Cinchna trees, 27, 30–31
Belgian Congo plantation of, 160–161
climate for growing, 27
fungus disease of, 160–161
plantations of, 30–31
Index

seeds of, 26–30
unavailable due to World War II, 70
varieties of, 28, 30
Cinchonidine, 28
Cinchonine, 28
Cinchonism, 51
Ciprofloxacin, 203
Circumsporozoite (CS) gene, cloning of, 228
Circumsporozoite protein, 228–230
Civil War, 44–45
Civil Works Administration, mosquito control program of, 45
Clark, William Mansfield, 80
Cleopatra, bed net of, 238
Cleveland, L. R., 138
Clindamycin, 196–197, 200, 202, 252
Clinical trials, prisoners used in, 121, 128–129
Clinton, Sir Henry, 46–48
Clostridium perfringens, 190
Clyde, David, 224–226
Coal tar
chemical composition of, 53–54
dyes synthesized from, 53–59
light oil fraction of, 53–54
for waterproofing, 53
Coartem tablets, 178–179, 251
Coatney, Robert G., 108–109, 128, 195–196
Coenzymes Q, 113–114
Coggleshall, L. T., 79–80, 90
Cohen, Joe, 231–232
Cohn, Ferdinand, 9
Colombia, Panama Canal
construction and, 40–41
Columbia University, DNA purification at, 153
Combination therapy, 140, 142, 146–148
artemisinin in, 177–178, 243–244, 250
dapsone in, 162
fosmidomycin-clindamycin, 200
lumefantrine in, 178
mefloquine in, 178, 253
piperaquine in, 250, 253
primaquine in, 132–133
pyrimethamine in, 140–141
quine in, 246–247
for resistance management, 162, 253
Communicable Disease Center, 45
Compendium of Materia Medica (Li Shihzen), 171
Complementary base pairing, of DNA, 153–155
Complementary DNA expression libraries, 156
Complex I, II, III, and IV, in parasites, 110–111
Compound 3666 (pyrimidine derivative), 105–106
Compound 3936 (pyrimidine derivative), 106
Compound 4430 (pyrimidine derivative), 106
Compound 4888 (pyrimidine derivative), 106
Conference of Berlin, on African colonial disputes, 38
Congo River, exploration of, 34–35
Cook, R., 201
Copper acetoarsenate, 206–207
Cornwallis, Major General Charles, 47–48
Councilman, W. T., 8
Countess’s bark or powder, 23, see also Cinchona bark
Covell, Sir Gordon, 209
Cox, R. A., 201
Creosote, 54
Crick, Francis, 153
Cromwell, Oliver, 25
Cuboni, Giuseppe, 4
Culex mosquitoes, 15
“Cultivation of Plasmodia and the Immunology of Malaria,” 138–139
Cultural Revolution, in China, 173
Culture
  of mosquitoes, 100
  of Plasmodium, 100–103, 169
Curd, Frank, 105
Cycloguanil, 97, 106–107, 162, 249
Cycloheximide, 196
2-Cyclohexyl-3-hydroxy-1,4-naphthoquinone (parvaquone), 114–117
3-(8-Cyclohexyl)-octyl-2-hydroxy-1,4-naphthoquinone, 112
Cytochrome c, 110–112
Cytoplasm, 185–186
Cytosomes, 185–186

D
da Cadamosto, Captain Alvise, 31–32
Dapsone, 142, 162
Daraprim, 97, see also Pyrimethamine
Darrow, Clarence, 120–121
Dave, Dilip, 110
Davey, Garnet, 105
DDT, for mosquito control, 45, 150–151, 210–212
de Kruif, Paul, 69–70
de la Calancha, Father Antonio, 24
de la Condamine, Charles Marie, 26–27
de Lesseps, Ferdinand, 40
de Lugo, Cardinal Juan, 24, 25
de Vega, Juan, 23–24
Delayed death, of parasites, 197
Deng Xiaoping, 169
1-Deoxy-d-xylulose-5-phosphate enzymes, 199
Desjardins, Robert E., 141, 146
Desowitz, Robert, 80
Developmental cycle, discovery of, 16–18
Developmental drugs, 253–254
DHA (dihydroartemisinin), 172, 176
2,3-Diamino-5-p-ethylpyrimidine, 97, see also Pyrimethamine
2,3-Diaminopyrimidine, 96
Diasone, 142
(α-Dibutylaminoethyl)-6,8-dichloro-2-(3’,4’-dichloro)phenyl-4-quinoline methanol, 143–144
Dichlorodiphenyltrichloroethane (DDT), for mosquito control, 45, 150–151, 210–212
N-Diethylamino-isopentyl-8-amino-6-methoxyquinoline (pamaquine), 66–68, 84, 122–125, 129–130, 135
Dihydroartemisinin (DHA), 172, 176
Dihydrofolate reductase, 98–99 antagonists of, 161–163, 249–250
Dihydrofolate synthase, in folate synthesis, 98–99
Dihydroneopterin aldolase, in folate synthesis, 98–99
Dihydroneopterin triphosphate, 103
Dihydroorotate dehydrogenase (DHODH), 110, 117–119
Dihydropteroate synthase, 92–93, 98–99, 162–163
Dimethylallyl pyrophosphate, 199
Dionisi, Antonio, 15
Dioxy-diamino-arseno-benzene, for syphilis, 62–63
DNA, 153–158
duplication of, 154
 genetic code of, 154–155
 isolation of, 156–157
 libraries of, 156–157
 nucleic acids in, 158
 of Plasmodium, 182–185
 of Plasmodium knowlesi, 183
 polymerase chain reaction method for, 157
 recombinant method of, 155–156
 sequencing of, 155, 157–158
 structure of, 153–154
 as transforming principle, 153
 Watson-Crick model of, 153–154
DNA polymerase, 157–158
Doering, William, 159–160
Doktor Phantasmus (Ehrlich), 63
Dolichols, 199
Domagk, Gerhard, 68, 81–89, 188
Don Quixote, 240–241
Doxycycline, 194, 202, 252
quinine with, 246–247
Drug resistance, see Resistance
Druilhe, Pierre, 237
Dubos, René, 191–192
Duisberg, Carl, 63–64, 83–84, 122
Dyes
  azo, 82–89
  natural, 55
  synthetic, see Synthetic dyes

E
East Coast fever (Theileria parva), 114
Ebers Papyrus, 2
Economic impact, of malaria, 253
Egypt, eradication program for, 211
Ehrlich, Ismar, 59, 121–122
Ehrlich, Paul, 7, 59–63, 72, 151
Elderfield, Robert C., 128
Eli Lilly, 193
Elion, Gertrude, 113–114
Elizabeth I (queen of England), 32
Emergency Relief Agency, mosquito control program of, 45
Emry, Etienne, 161
England
  African exploration and colonization by, 32–39
  domination of ocean travel by, 39–40
  industrialization in, coal tar produced during, 52–53
  malaria introduction from, 42–43
  organic chemistry interest in, 55
  pamaquine development in, 126–127
  proguanil work in, 104–108
  pyrimethamine development in, 94–104
  quinine in, 25–26
  synthetic dye industry in, 56–59
5-Enolpyruvylshikimate 3-phosphate synthase, 199
Entozon (9-aminoacridine), 68
Enzymes, altered or amplified, in resistance, 152
Epidemiology, of malaria, 253
Epstein, J. E., 234
Eradication programs, see also Mosquito control
  in American South, 45–46, 206
  antimalarial drugs for, 212–213
  challenges to achieving, 240–244
  chloroquine for, 80
  DDT for, 210–212
  in Egypt, 211
  expectations for, 240–244
  in Germany, 208–209
  Global Malaria Eradication Campaign, 150
  in Italy, 48–50, 206–207, 211
  mathematical models for, 207–208
  in Panama, 39–42, 205–206
  reasonable strategies for, 245–256
  in South America, 209–210
  UNICEF involvement in, 211
  vaccines for, see Vaccines
  World Health Assembly for, 212–213
Erion, 68
Erythromycin, 194
Ethambutol, 194
Eukaryotes, 185
Evolution, resistance and, 152
Exoerythrocytic forms, 20–21
Eyles, Don E., 214–215

F
Fairley, Neil Hamilton, 19, 73–74, 108
Falco, Elvira, 96–97
Fansidar (sulfadoxine-pyrimethamine), 140–141, 143, 149, 162, 178, 249–250
Fansimef, 141, 149
Farbenfabriken vorm. Friedrich Bayer and Co., 83

Downloaded from www.asmscience.org by
IP: 54.70.40.11
Farr and Kunzel quinine manufacturers, 28
Fatty acid synthase system, 198
Fatty acid synthesis, in parasites, 197–198
Feldman, William, 192–193
Feletti, R., 64
Fernex, Michel, 141, 144–146
Ferriprotoporphyrin IX, 165–166
Fever trees, see Cinchona trees
Fidock, David, 166–167
Fieser, L. F., 112
Fildes, Paul, 89–90
Finlay, Carlos, 41
Fiske, Cyrus J., 94
Fitch, Coy, 164–165
Fleming, Alexander, 188–191
Florey, Howard, 189–191
Folates
metabolism of, 99–104
synthesis of, 98–99, 198–199
Fonseca, Gabriel, 24
10-Formyltetrahydrofolate synthase, 99
Forneau, Ernest, 87–89, 142
Fosmidomycin, 199–200, 252
Franks, Bobby, murder of, 120–121
Friedman, Milton, 101–102
Fry, M., 110–111
FSV-1 vaccine, 230–231
FSV-2 vaccine, 231
Fujisawa Pharmaceuticals Company, 199–200
Fumigation, of homes, 208–209

G
Gambia, National Impregnated Bednet Programme for, 239
Gambia River, exploration of, 33
Game hunting, in Africa, 39
Gametes
antibodies to, 215–216
proteins of, 214, 216, 217–218
Garnham, P. C. C., 20
Gates, Bill and Melinda, see Bill and Melinda Gates Foundation
Ge Hang, 171
Geary, Timothy, 196
Gebbers, Horst, 161
Geissen University, 53
Gel electrophoresis, in DNA analysis, 158
Gelmo, Paul, 87
Gene amplification, in resistance, 152
Gene expression libraries, 156
Genentech, vaccine patent of, 228–229
Genetic engineering, for artemisinin production, 180
Gerhardt, C., 6
Germany
antimalarial drug industry in, 121–126
eradication programs in, 208–209
industrialization in, coal tar produced during, 52–53
Prontosil development in, 82–87
synthetic dye industry in, 53–68
Giemsa, Gustav, 61–62, 208–209
Glaxo Pharmaceuticals, 190
Global Eradication of Malaria Program (1960s), 244
Global Eradication Program, 80
Global Fund to Fight AIDS, Tuberculosis, and Malaria, 240
Global Malaria Eradication Campaign, 150
Glucose-6-phosphate dehydrogenase, hemolytic anemia due to, 129, 132, 136
Glucosulfone, 142
Glycerol-3-phosphate dehydrogenase, 111
Glycoproteins, of parasites, 167
Glyphosate, in shikimate pathway inhibition, 199
Godson, Nigel, 228
Gold sodium thioglycollate, 85
Goldwater Memorial Hospital, Atabrine work at, 71–72
Golgi, Camillo, 7–8
Gomes, Bernardino, 28
Good Manufacturing Practices, for artemisinin, 169–170
Goodwin, Leonard, 96–97
Gordon, Daniel, 230–231
Gorgas, Major William C., 41–42, 205–206, 209
Gramicidin, 192, 195
Grassi, Giovanni Battista, 15–18, 64
Greenberg, Joseph, 195–196
Greenwood, B. M., 235
GTP cyclohydrolase, 98–99, 103
Guerra, Francisco, 50
Gutteridge, Winston, 110, 117, 183
Guttmann, Paul, 61, 121
Gwadz, Robert, 215, 228

H
Hackett, Lewis H., 206–207
Haemoproteus, 68
Hahn, Fred, 165
Halofantrine, 249
Hamburg Tropical Institute, 64
Handbook of Prescriptions for Emergency Treatment (Ge Hang), 171
Harrison, Gordon, 50
Harvard University, sulfa drug work at, 90
Hasskarl, Justus, 29
Hata, Sahachiro, 63
Hawking, Frank, 164–165
Hawkins, John, 32
Hay-Bunau-Varilla Treaty, 40–41
Heatley, Norman, 189
Hemolytic anemia, primaquine-induced, 129, 132, 176
Hemozoin, 165, 173
Henry the Navigator of Portugal, 31–32
Heppner, Gray, 231–232
Herd immunity, 214
Higginson, Betty, 201
Hinshaw, Corwin, 192–193
Hippocrates, 2
Hitchings, George, 94–97
Hitler, Adolf, 81
Ho Chi Minh, 171
Hoechst Dyeworks, 62, 67, 83, 85
Hoffman, Stephen, 230, 236–238
Hoffmann-La Roche
  African involvement of, 161
  Fansidar development at, 143
  mefloquine work at, 141
Hofmann, August, 53–59, 179
Holofernes, Assyrian general, bed net of, 238
Holz, George G., 197
Homer, 2
Homewood, C. A., 165
Hookworm control, 206
Hopkins, Johns, 9, see also Johns Hopkins University
Horlein, Heinrich, 122
Hotchkiss, Rollin, 192
Hudson, Alan, 114–115
Huff, Clay G., 19–20
Hybridomas, in vaccine development, 216–217
2-Hydroxy-3-alkynaphthoquinone, 112
Hydroxychloroquine, 246
Hydroxymethyl dihydropterin pyrophosphokinase, in folate synthesis, 98–99
3-Hydroxy-1,4-naphthoquinone (BW58C), 115
Hydroxynaphthoquinones, 112–113
Hynozoites, 20–21

I
I.G. Farbenindustrie
  Atabrine development at, 69–70
  formation of, 83
  Prontosil development at, 82
  quinine development at, 31
  synthetic dye development at, 63–64
Ilan, Joseph and Judith, 200–203
Illuminating gas production, coal tar by-product from, 52–53
Immunity, to malaria, in native Africans, 32–33, 38–39, 44
Imperial Chemical Industries
Atabrine discovery by, 70
penicillin development by, 190
proguanil discovery by, 104–105
Impermeability, of parasites, to
drugs, 152
“Impossible dream” aspect, of
eradication, 240–241
Incubation period, 19–20
India
eradication programs in, 209
measles vaccine program in, 243
mosquito control in, 205
Indian Medical Service, 205
Indian tonic water, 51
Indians, Peruvian, cinchona bark preparations of, 23, 50–51
Industrialization, coal tar produced
during, 52–53
Inheritance, of resistance, 152–158
Insecticides
for bed nets, 239
for breeding sites, 206–207
DDT, 45, 150–151, 210–212
pyrethrins, 45, 208–211
Institute for Infectious Diseases,
Berlin, 62
Institute for Maritime and Tropical Disease, Hamburg, 61–62
Institute for OneWorld Health, 237
International Health Division, of
Rockefeller Foundation,
206–207
International Task Force for Disease Eradication, 241–242
Irradiation, of sporozoites, for
vaccine, 222, 224–227
Isoniazid, 194
Isopentaquine, 127–129
Isopentenyl pyrophosphate units, 199
Isoprenoid, synthesis of, 199
Italy
bonification of, 48–50
eradication programs in, 48–50,
206–207, 211
quinine in, 48–49
J
Jacobs, Walter, 128
Jacobus, Captain David P., 139
James, Sydney Price, 19–20, 205
Java, cinchona trees in, 30–31, 70
Jenner, Edward, 241–242
Jensen, James, 100–101, 169, 196
Jesuit’s bark or Jesuit’s powder, 24–26, 56, see also Cinchona bark;
Quinine
Johns Hopkins University, 126
parasite discovery at, 7, 8
quinine work at, 70–71
sulfa drug work at, 91
Journal of an Expedition to Explore the Course and Termination of the Niger (Lander), 34
K
Kapuscinski, Ryszard, personal
description of symptoms, 1
Karolinska Institute, 81
Keasling, Jay D., 180
Keith, Minor, 125
Kekulé, August, 54–55, 58, 63
Kemball Bishop and Company, 190
Kentish disorder, 42–43
Kikuth, Walter, 68
Kilejian, Araxie, 183–184
Kina Bureau (quinine cooperative), 30–31
Kitasato, Shibasaburo, 63
Klarer, Joseph, 84–86
Klayman, Daniel, 173–174
Klebs, Edwin, 4
Koch, Robert, 4, 16–18, 48–49, 62
Köhler, Georges, 216–217
Kopanis, P., 64
Korean War, primaquine in, 129–133
L
Laird, McGregor, 34
Lake Ngami, 35–36
Lake Nyasa, 37
Lake Tanganyika, 37
Lancefield, Rebecca, 84
Land, Edward, 160
Lander, John, 33–34
Lander, Richard, 33–34
Lap-Dap (chloroproguanil-dapsone), 162, 250
Lapinone, 112–113
Lapudrine, 250
Lariam, 148–149, see also Mefloquine
Larvicides, 45, 205–206, 210
Laveran, Charles-Louis Alphonse, 5–9
League of Nations Health Organization, Malaria Commission of, 125
Ledger, Charles, 29–30, 160
Ledger, George, 30
Leopold (prince of Belgium), 160–161
Leopold, Nathan, 120–121, 128–129
Lepetit Pharmaceuticals, 194–195
Li Shihzen, 171
Liang, X. T., 172–173
Libraries, DNA, 156
Life cycle, 21–22
Ligase, in DNA technology, 155–156
Light oil fraction, of coal tar, 53–54
Lincomycin, 196–197
Lipoic acid, in fatty acid synthesis, 198
Lips, Marcel, 221
Liver, parasites in, 18–22
primanique for, 121–136
tafenoquine for, 133–136
Liverpool School of Tropical Medicine, 147–148, 204–205
Livingstone, David, 35–37
“Livingstone Prescription,” 36
Loeb, Richard, 120–121
London School of Hygiene and Tropical Medicine, 146
Loucq, Christian, 238
Louis XIV (king of France), 26
Lumefantrine, 178, 250–251
Lysosomes, drug accumulation in, 165
M
MacArthur, General Douglas, 72
MacCallum, William, 9, 68, 124
MacDonald, George, 207–208
Macintosh, Charles, 54
Mackenzie, Bishop Charles, 37
MacLeod, Colin, 152–153, 182
“Magic bullets,” of Ehrlich, 60
The Malaria Capers (Desowitz), 80
Malaria Commission (Royal Society), 205
Malaria Institute, India, 209
Malaria pigment, 164–166
Malaria Service of the Northeast, 210
Malaria Vaccine Initiative, 233
Malaridine, 251
Malarone (proguanil-atovaquone), 108, 116, 162, 252
Malate-quinone oxidoreductase, 111
Maloprim (dapsone), 142
Maltbie Chemical, 187–188
Mamani, Manuel Incra, 30, 160
The Man of La Mancha, 240–241
Manhattan Project, 70
Man’s Mastery of Malaria (Russell), 245
Mansfield, William, 126
Manson, Patrick, 10–11, 15
Mao Zedong, 171
Marchiafava, Ettore, 6–8, 159
Marmur, Julius, 182–183
Marshall, Eli K., 71–72, 77, 91
Marshes, see Wetlands and mosquito breeding sites
Mast cells, stain for, 59
Mathematical models, malaria control, 207–208
Mauss, Hans, 67
Mauveine dye, 58
Mayo Clinic, streptomycin research at, 192
M&B 693 (sulfapyridine), 88
McCarty, Maclyn, 152–153, 182
Measles, eradication campaign for, 242–243
Medical Research Council, 104, 190
Medicines for Malaria Venture, 133–134, 250
Mefloquine, 137–149, 248–249
  in combination therapy, 178, 253
development of, 137–144
disadvantages of, 148–149
  mechanism of action of, 144
  resistance to, 148–149, 167
  structure of, 144
Meissner, Wilhelm, 28
Menoctone, 112, 114
Mepacrine, 68
Mephaquine, 148, see also Mefloquine
Merck, George, 192–193
Merck Company, 188, 192
Merkli, B., 141
Merozoites, antibiotic effects on, 202
Messenger RNA, in DNA
duplication, 154–155
Methemoglobinemia, from
pamaquine, 125
Method for Curing Fevers (Sydenham), 25
6-Methoxyaminoquinolone, 65–66
Methylene blue, 59–63, 65
  primaquine development from, 121–133
  structure of, 135
  tafenoquine derived from, 134–135
5,10-Methylene tetrahydrofolate
dehydrogenase, 99
Mexican War, troops returning from, 44
Microbe Hunters (de Kruif), 69–70
Microgamete immobilization
reaction, 215
Mietsch, Fritz, 67, 85–86
Miller, F. W., 201–202
Miller, Louis, 234
Milstein, Cesar, 216–217
Missionary Society for the Extinction
of the Slave Trade and the
Civilisation of Africa, 35
Missionary Travels (Livingstone),
36–37
Mithridates, 151
Mitochondria, of parasites, 109–112,
  185–186
Molecular photocopying, 157
Monkey malaria, see Primate malaria
Monoclonal antibodies
to circumsporozoite protein, 228
  for vaccines, 216–217
Mosquito(es)
in American South, 42–46
  parasite discovery in, 9–18
Mosquito control, 205–213
  in American South, 206
  bed nets for, 206, 238–239, 243–244
  DDT for, 45, 150–151, 210–212
  in early 20th century, 45–46
  fumigation for, 208–209
  in Italy, 206–207, 211
  mathematical models for, 207–208
  in Panama Canal, 39–42, 205–206
  pyrethrum sprays for, 208–210
  Ross work on, 204–205
  in South America, 209–210
Most, Harry, 221–222, 226
Mouse malaria, 115, 158, see also
  Plasmodium berghei
  antibiotics for, 195–196
  research on, 221
  vaccine for, 222–223
Müller, Paul, 210
Mulligan, H. W., 220, 222
Multidrug resistance, 167
Multiplier of the disease, in
  mathematical model, 207
Murray, Mungo, 35
Mussolini, Benito, 49
Mutations, 155
N
NADH-ubiquinone oxidoreductase,
  110–111
Nagana red dye, 62
Naphthoquinones, 112–117
National Cancer Institute, 73
National Impregnated Bednet
  Programme, for Gambia, 239
National Institute of Agricultural Botany, Cambridge, 180
National Institute for Medical Research, London, 183
National Institutes of Health
Atabrine research at, 73
PfCRT gene work at, 166
vaccine work at, 215
National Medical Research Institute, vaccine work at, 222
National Research Council, 70, 76
National Research and Development Corporation, 217
Natural selection, resistance and, 152
Naval Medical Research Institute, 222–223
Nei Ching, 2
Nepal, vaccination program in, 243
Nets, bed, 206, 238–239, 243–244
New York University, CS gene patent of, 228–229
Niger River, exploration of, 33–35
Nitroakridin 3582 (9-aminoacridine), 68
Nobel Prize for Physics (1980), 157
for Physiology or Medicine (1939), 81–82, 188
for Physiology or Medicine (1945), 190–191
for Physiology or Medicine (1952), 193
for Physiology or Medicine (1984), 216
for Physiology or Medicine (1988), 94
Nocht, Bernard, 61
Nucleic acid(s), see also DNA
RNA, in DNA duplication, 154–155
synthesis of, in parasites, 109
Nucleotides, in DNA, 153–154
Nucleus, 185–186
Nun’s Priest’s Tale (Chaucer), 3
Nussenzweig, Ruth, 222–224, 228–229
Nussenzweig, Victor, 228–229

O
“Office 523” artemisinin project, 171
Office of National Defense Malaria Control Activities, 45
OneWorld Health, 180
Oocysts, discovery of, 14
Ookinetes, proteins of, 214, 216
Opie, Eugene, 68
Organelles, 185–186
Organic Chemistry and Its Application to Agriculture and Physiology (Leibig), 53
Orotidine-5′-monophosphate pyrophosphorylase, 109
Oscillaria malariae, 6
Osler, William, 8, 9
Oswell, William, 35

P
Paludrine, 104, 146, see also Proguanil
Pamaquine (plasmoquine, plasmochin), 66–68, 84, 122–125, 129–130, 135
Panama Canal, 39–42, 205–206
para-Aminobenzenesulfonamide, 85–86, 89–93
para-Aminobenzoic acid antagonists of, 249–250
synthesis of, 198–199
para-aminosalicylic acid, 194
Paresis, syphilitic, 66
Paris green, 206–207, 210
Park, Mungo, 33–34
Parke-Davis, 193–194
Parvaquone, 114–117
Pasteur, Louis, 4
Pasteur Institute of Algeria, 220–221
Pasteur Institute of Paris, 87–88, 142
Pasteur Institute of Southern India, 220
Pelletier, Pierre, 27–28
Penicillin, 188–191
Penicillin G, 190
Penicillium chrysogenum, 190
Penicillium notatum, 188, 190
Pentaquine, 121, 127, 249

Downloaded from www.asmscience.org by
IP: 54.70.40.11
Pentosam, 97
Perkin, William, 56–58, 160
Permethrin, for bed nets, 239
Peruvian bark, 24, see also Cinchona bark
Peters, Wallace, 140, 146–148, 165, 169
PfCRT gene, 166
PfMDR gene, 167
Pfs48/45 protein, of *Plasmodium falciparum*, 218–219
Pfs230 protein, of *Plasmodium falciparum*, 218–219
Pgs25 protein, of *Plasmodium gallinaceum*, 218–219
Pgs28 protein, of *Plasmodium gallinaceum*, 218–219
Pharmakina, 160–161
Phenazopyridine, 85
Pigment, malaria, 164–166
Piperaquine, 250, 253
α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinoline methanol, 143–144, see also Mefloquine
α-(2-Piperidyl)-6,8-dichloro-2-phenylquinoline methanol, 143–144
Pitch, from coal tar, 54
Plasmids, in DNA technology, 155–156
Plasmodochin (pamaquine), 66–68, 84, 122–125, 129–130, 135
*Plasmodium*
DNA of, 182–185
as eukaryote, 185
life cycle of, 185, 187
numbers in average patient, 152
pigment accumulation in, 164–166
ribosomes of, 200–202
ring stages of, 176
size of, 185
structure of, 185–186
*Plasmodium berghei*
antigens of, 227–228
BW556C naphthoquinone for, 115
chloroquine accumulation in, 164
discovery of, 221
qinghaosu for, 171–172
in Rane test, 139–140
research on, 221–223
ribosomes of, 200–201
sporozoite antigens of, 228
ubiquinones of, 113
vaccine for, 222–223
*Plasmodium cathemerium*, 195
*Plasmodium cynomolgi*
mefloquine for, 142
primaquine for, 128
qinghaosu for, 172
sporozoite antigens of, 228
tafenoquine, 134
ubiquinones of, 113
vaccine for, 223–224
*Plasmodium falciparum*
antibiotics for, 196–197
artemisinin for, 252
atovaquone for, 116
BW556C naphthoquinone for, 115
chloroquine accumulation in, 165
chloroquine resistance transporter, 166
chromosomes of, 155, 158
circumsporozoite protein of, 229
culture of, 100–103, 169
DNA structure in, 158
fatty acid synthesis in, 197–198
fosmidomycin for, 200
genoeme of, 158
lethality of, 66
life cycle of, 21–22
mefloquine for, 140
mutation rate of, 252–253
proguanil for, 108
proteins of, 218, 219
pyronaridine for, 251
qinghaosu for, 172, 174
quinine for, 247
resistance in, 143–144, 159, 252–253
artemisinin, 176–178
chloroquine, 133, 151
mefloquine, 167
sulfadiazine for, 90
tafenoquine for, 134
vaccine for, 226, 229–230
in Vietnam War, 137–141
Plasmodium gallinaceum
1-p-chloroanilinopyrimidine for, 105
drug actions in, 108–109
proteins of, 217–218
sulfanilamide for, 90
tyrothricin for, 195
vaccine for, 214–221
Plasmodium knowlesi
antibiotics for, 196
DNA of, 183
proteins of, 218
ribosomes of, 201
sporozoite antigens of, 228
vaccine for, 223–224
Plasmodium lophurae, 77–78
antibiotics for, 196
culture of, 100
DNA of, 182–183
fatty acid synthesis in, 197–198
folate metabolism in, 99–100
naphthoquinone for, 112
nucleic acid synthesis in, 109
pentaquine for, 127
ribosomes of, 201–202
sulfonamides for, 91–92
ubiquinones of, 113
Plasmodium malariae, pyronaridine for, 251
Plasmodium ovale, pyronaridine for, 251
Plasmodium relicitum, 64, 220–221
Plasmodium vivax
immunity to, 219
in Korean War, 131
lapinone for, 112–113
methylene blue for, 121–122
pentaquine for, 127–128
primaquine for, 128–129
proguanil for, 108
proteins of, 219
pyronaridine for, 251
qinghaosu for, 172, 174
SN-10275 for, 143–144
sulfadiazine for, 90
tafenoquine for, 134
tyrothricin for, 195
Plasmodium yoelii
BW556C naphthoquinone for, 115
genome of, 158
Plasmoquine, 66–68, 84, 122–125, 129–130, 135
Plastids
apical, 187–203
plant, functions of, 198–199
Platzer, Edward, 98, 99–100
Plimmer, H. G., 10
Pneumonia, streptococcal, sulfapyridine for, 88–89
Polaroid Corporation, 160
Polio, eradication of, 242
Polymerase chain reaction, 157
“Poor man’s quinine,” 28
Portugal, exploration by, 31–32
Potassium chromate, in allyltoluidine synthesis, 57
Potter, Michael, 217
“Powder of the Most Eminent Cardinal de Lugo,” 24
President’s Malaria Initiative, 240
Preston, Andrew, 125
Primaquine, 66, 121–136, 249
chloroquine with, 131–132
in combination therapy, 132–133
development of, 121–128, 135
hemolytic anemia due to, 129, 132
human testing of, 128–129
for Korean War veterans, 129–131
mefloquine for, 142
mechanism of action of, 129–131
structure of, 131–132
for Primate malaria
folate metabolism in, 99–100
mefloquine for, 142
parasite DNA in, 183
pentaquine for, 127
primaquine for, 128
Primate malaria (Continued)
qinghaosu for, 172
sulfanilamide for, 90
tafenoquine for, 134, 136
vaccines for, 218–219, 223–224
Prince Leopold Institute of Tropical Medicine, Antwerp, 221
Principles of Soil Microbiology
(Waksman), 191
Prisoners, for drug trials, 121, 128–129
Program for Appropriate Technology in Health (PATH), 233, 238
Proguanil, 104–108, 146, 250, 252
atovaquone with (Malarone), 108, 116, 162, 252
mechanism of action of, 108–112
Prokaryotes, 185
Prontosil, 82–93
antimalarial action of, 90–92
bioactivation of, 88
development of, 82–89
efficacy of, 87–92
mechanism of action of, 89–90, 92–93
Nobel Prize for, 81–82
structure of, 82
Purines, in DNA, 153
Puromycin, 196
Purple dyes, aniline, 58
Pyrazinamide, 194
Pyrethrum, 45, 208–211
Pyridium (phenazopyridine), 85
Pyrimethamine, 98–100, 249
in combination therapy, 140–141
development of, 94–97
dosage for, 97–98
mechanism of action of, 98–104, 108–112
resistance to, 162–163
structure of, 97
sulfadoxine with (Fansidar), 140–141, 143, 149, 162, 249–250
testing of, 97–98
Pyrimidines
in DNA, 153
metabolism of, 109–110
pyrimethamine development from, 95–97
Pyronaridine, 251
Pyruvate dehydrogenase, in fatty acid synthesis, 198
Q
Qinghaosu, see Artemisinin (qinghaosu)
Qinghaosu Antimalarial Coordinating Research Group, 174
Quillaja saponaria, 232
Quinacrine, see Atabrine
“Quina-quina,” 23
Quinidine, 28
Quinine
adverse reactions to, 247
African exploration and exploitation related to, 31–39
in American Revolution, 48
bark producing, see Cinchona bark
chemical properties of, 50–51
in combination therapy, 246–247
current production of, 160
discovery of, 246
drugs derived from, 247
dye industry development from, 56–57
efficacy of, 247
in England, 25–26
entry to Europe, 24
extraction of, 28–29
formulations containing, 28, 36, 50–51, 161
intravenous administration of, 161, 247
isolation of, 27–28
in Italy, 48–49
mechanism of action of, 50–51, 161
vs. mefloquine, 142
mefloquine development from, 137–149
overdose of, 51
pamaquine with, 125
for Panama Canal construction, 39–42
Peruvian Indian use of, 23, 50–51
"poor man’s,” 28
production of, 30–31
pyrimidine replacements for, 97
resistance to, 159, 246
seeds of, 26–30
shortage of, 56
structure of, 57
synthesis of, 56–57, 159–160
in tonics, 51
trees producing, see Cinchona trees
use in Peruvian colony, 23–24
Quinolines, 65–66, 123
Quixotic aspect, of eradication, 240–241

R
Radiation Laboratory, 70
Radiation treatment, of sporozoites, for vaccine, 222, 224–227
Rane test, 139–140
Recipe for 52 Kinds of Diseases (ancient Chinese book), 171
Red fuchsin stain, 59–60
Reed, Major Walter, 41
Reproductive ratio, in mathematical model, 207–208
Resiliency, in resistance, 152
Resistance, 150–167, 252–253
to antifolates, 161–163
to artemisinin, 176–178
to chlorcycloguani, 162
to chloroquine, 133, 137–149, 150, 164–166, 248–249
to cycloguani, 162
definition of, 151–152
to dihydrofolate reductase inhibitors, 161–163
history of, 151–152
inheritance of, 152–158
mechanisms of, 152
to mefloquine, 148–149, 167
multidrug, 167
in *Plasmodium falciparum*, see *Plasmodium falciparum*, resistance in
to pyrethroids, 244
to pyrimethamine, 162–163
to quinine, 159, 246
to sulfamethoxazole, 162
to sulfathiazole, 162
in trypanosomes, 162
Resochin, 77, 79
Restriction enzymes, 155–156
Reverse transcriptase, 156
Revolutionary War, malaria situation before and during, 43–48
Riamet, 178, 251
Ribosomes, of *Plasmodium*, 200–202
Richard, E., 6
Richards, W. H. G. (Harry), 110, 146
Richle, R. W., 141
Rieckmann, Karl, 226
Riedel, J. D., 28
Rifampin, 194–197, 202
Rifamycins, 195
Risk factors, for malaria, 245
River Niger, exploration of, 33–35
RLF vaccine, 231
RNA, in DNA duplication, 154–155
RNA polymerase, rifampin effects on, 202
Robinson, Robert, 104, 126
Rockefeller, John D., 206
Rockefeller Foundation, establishment of, 206
Rockefeller Institute
DNA studies at, 182–183
drug resistance studies at, 152–153
folate studies of, 99, 100
hookworm eradication program of, 206
penicillin discovery, 189, 191
sulfanilamide development at, 84
Rockefeller Sanitary Commission, 206
Rodent malaria, folate metabolism in, 99–100
Roehl, William, 62–65, 84
canary assay of, 122–124
Roll Back Malaria Partnership, 240
Roman fever, 2–3
Romanowsky, Dimitri, 61
Rose, Frank, 105
Rosengarten & Sons, quinine manufacturers, 28
Ross, Ronald, 9–18, 51, 64, 121, 204–205, 207, 210
Ross Institute, Ceylon, 207
Roth, Barbara, 96–97
Roundup weedkiller, in shikimate pathway inhibition, 199
Royal College of Chemistry, synthetic dye research at, 55–58
Royal Prussian Institute for Experimental Therapy, 62
RTS,S vaccine, 230–235
Rubiazol, 87
Russell, Paul F., 220–222, 245
Russell, Peter B., 97
Rutgers Research and Endowment Foundation, 193
Sadun, Elvio, 138–139
Salvarsan (606 derivative), for syphilis, 62–63
Sanaria company, 236–238
Saner, Frederick, 157–158
Sanochrysine, 85
Sanofi-Aventis, 180
Scaife, John, 183
Schatz, Albert, 192–193
Schaudinn, Fritz, 19
Schellenberg, K. A., 108–109
Schmidt, Leon H., 127–128
Schnitzer, Robert, 67, 84
Schoenhofer, Fritz, 122
Schulemann, Werner, 122–123
Schweppes quinine beverages, 51
Seasonality of disease, 2–3, 25
Second Quinine Convention, 30–31
Sensi, Piero, 194–195
Septicemia, streptococcal, 84
Sergent, Edmond, 220–221
Sergent, Etienne, 220–221
Serine hydroxymethyltransferase, 99–100
Serum and Vaccine Institute, Beijing, 169
Shakespeare, William, 3
Shanghai Institute of Material Medica, 174
Shanghai Pharmaceutical Industry Research Institute, 250
Shannon, James A., 71–72, 126
Shikimate pathway, 198–199
Shortt, H. E., 20
Sigma-Tau Pharmaceuticals, 175–176, 250
Sioli, Franz E., 66, 124–125
606 derivative, for syphilis, 62–63
Slaves in American South, 43–44
trading in, 32–35
Sleeping sickness, 62–63
Smallpox, eradication of, 240–242
Smith, Homer, 71
SN-7618 (chloroquine), 76–79, 126
SN-10275 and analogs, 143–144
SN-13276 (pentaquine), 121
Society of Jesus, quinine trade of, 24
Solasulfone, 142
Somalia, last smallpox case in, 242
Sontochin, 77–79
Soper, Fred L., 209–211
South America, mosquito control in, 209–210
South East Asian Quinine Artesunate Malaria Trial Group, 175
Special Programme for Research and Training in Tropical Diseases artemisinin program of, 168–170
mefloquine program of, 140, 145, 148
Speke, John Hanning, 37
Speyer, Franziska, 62
Speyer House, research at, 62–64
Sporozoites antigen of, 227–230
discovery of, 219
vaccines using, 220–230
Spraying, for mosquito control, 208–209
Squibb Institute for Medical Research, 72–73
Stanley, Henry Morton, 37
Sterling Drug Company, 70
Sternberg, Major George, 4–5, 7
Stevens, Ash, 133
Stolen subparticle hypothesis, 201–202
Streptococcal infections, sulfonamides for, 84, 86–89
*S. alboniger*, 196
*S. aureofaciens*, 194
*S. erythraeus*, 194
*S. griseus*, 192, 196
*S. lavendulae*, 199–200
*S. lincolnensis*, 197
*S. mediterranei*, 195
*S. venezuelae*, 193–194
Streptomycin, 191–197
Streptozon, 86
Succinate-ubiquinone oxidoreductase, 110–111
Suez Canal, construction of, 40
Sulfa drugs, 89
Sulfadiazine, 188
Sulfadoxine, 142–143
Sulfadoxine-pyrimethamine (Fansidar), 140–141, 143, 149, 162, 178, 249–250
Sulfamethazine, 188
Sulfamethoxazole, 162
Sulfamido-chrysoidine, 86, see also Prontosil
Sulfapyridine, 88
Sulfathiazole, 162, 188
Sulfadoxine, 142–143
Sulfonamides, 85–93, see also Prontosil
development of, 142–143
Survival of the fittest, resistance and, 152
Svartz, Professor N., 81
Swamps, see Wetlands and mosquito breeding sites
Sweet wormwood, see *Artemisia annua*; Artemisinin (qinghaosu)
Sydenham, Thomas, 25
Symptoms, historical description of, 1–4
Synthetic dyes
Atabrine, 67–76
chemotherapeutic applications of, 61–66
chloroquine derived from, 76–80
from coal tar, 53–59
histologic stains from, 59–62
Syphilis, arsenicals for, 62–63
T
Tafenoquine, 133–136, 249
Talbor, Robert, 25–26, 50–51
Taliaferro, William Hay, 195
Tar, coal, dyes synthesized from, 53–59
Targett, G. A., 235
Tellem (city in Africa), 33
Tennessee Valley Authority, mosquito control program of, 45–46
Terramycin, 194
Tetracyclines, 194, 196–197, 202, 246–247
Tetrahydrofolate inhibitors, 92–93, 96–103, 109
Textile industry, dyes for, 55–56
Thayer, William S., 9
*Theileria parva*, 114
Thiamine pyrophosphate, in fatty acid synthesis, 198
Thiomactomycin, 198
Thiostrepton, 202
*Through the Looking Glass* (Carroll), 245
Thymidine, 96
Thymidylate synthesis cycle, 98, 99, 103, 109
Tigertt, Colonel William, 138–139
Tommasi-Crudeli, Corrado, 4
<table>
<thead>
<tr>
<th>Term</th>
<th>Page(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totaquine</td>
<td>28, 160–161</td>
</tr>
<tr>
<td>Tourism, in Africa</td>
<td>39</td>
</tr>
<tr>
<td>Trafalgar, Battle of</td>
<td>56</td>
</tr>
<tr>
<td>Trager, William</td>
<td>99–102, 138, 169, 182–183</td>
</tr>
<tr>
<td>Transfer RNA, in DNA duplication</td>
<td>154–155</td>
</tr>
<tr>
<td>Transforming principle</td>
<td>153, 182</td>
</tr>
<tr>
<td>Transmission, blocking</td>
<td>see also</td>
</tr>
<tr>
<td>Mosquito control; Vaccines history of</td>
<td>204–205</td>
</tr>
<tr>
<td>Travels in the Interior Districts of Africa (Park)</td>
<td>33</td>
</tr>
<tr>
<td>Treaty of Paris</td>
<td>48</td>
</tr>
<tr>
<td>Triclosan</td>
<td>198</td>
</tr>
<tr>
<td>Trigg, Peter</td>
<td>168–169, 171, 183</td>
</tr>
<tr>
<td>Trimethylthionine stain</td>
<td>61–62</td>
</tr>
<tr>
<td>Trotter, H. D.</td>
<td>34</td>
</tr>
<tr>
<td>Trypanosomes</td>
<td>resistance in, 151</td>
</tr>
<tr>
<td>stains for, 62–64</td>
<td></td>
</tr>
<tr>
<td>Tryparsamide</td>
<td>128</td>
</tr>
<tr>
<td>Tu, Youyou</td>
<td>171–172</td>
</tr>
<tr>
<td>Tubercle bacilli, acid-fast stains for</td>
<td>60</td>
</tr>
<tr>
<td>Tuberculosis, antibiotics for</td>
<td>191–195</td>
</tr>
<tr>
<td>Tuckey, James</td>
<td>34</td>
</tr>
<tr>
<td>Tyrothricin</td>
<td>191–192, 195</td>
</tr>
<tr>
<td>Ubiquinol-cytochrome c</td>
<td>110</td>
</tr>
<tr>
<td>oxidoreductase</td>
<td></td>
</tr>
<tr>
<td>Ubiquinones</td>
<td>111, 113, 198–199</td>
</tr>
<tr>
<td>United Fruit Company, drug trials at</td>
<td>125</td>
</tr>
<tr>
<td>United Nations Children’s Fund</td>
<td>211–212</td>
</tr>
<tr>
<td>(UNICEF)</td>
<td></td>
</tr>
<tr>
<td>United Nations Relief and Rehabilitation Administration</td>
<td>211–212</td>
</tr>
<tr>
<td>University of California</td>
<td>antibiotic research at, 200–201</td>
</tr>
<tr>
<td>University of Chicago, primaquine research at</td>
<td>121, 128</td>
</tr>
<tr>
<td>University of Maryland, vaccine development at</td>
<td>224–226</td>
</tr>
<tr>
<td>University of Minnesota, vaccine work at</td>
<td>231</td>
</tr>
<tr>
<td>University of Münster</td>
<td>83</td>
</tr>
<tr>
<td>V Vaccines</td>
<td>213–238</td>
</tr>
<tr>
<td>altruistic</td>
<td>214</td>
</tr>
<tr>
<td>child trials of</td>
<td>233–234</td>
</tr>
<tr>
<td>development of</td>
<td>214–220</td>
</tr>
<tr>
<td>future of</td>
<td>235–238</td>
</tr>
<tr>
<td>immunity memory in</td>
<td>215–216</td>
</tr>
<tr>
<td>monoclonal antibodies for</td>
<td>216–217</td>
</tr>
<tr>
<td>for primate malaria</td>
<td>218–219, 223–224</td>
</tr>
<tr>
<td>protein identification for</td>
<td>216–219</td>
</tr>
<tr>
<td>RTS,S</td>
<td>230–235</td>
</tr>
<tr>
<td>sporozoite</td>
<td>220–230</td>
</tr>
<tr>
<td>subunit</td>
<td>230–235</td>
</tr>
<tr>
<td>van den Berghe, Louis</td>
<td>221</td>
</tr>
<tr>
<td>Van Noorden, Richard</td>
<td>181</td>
</tr>
<tr>
<td>Vanderberg, Jerome</td>
<td>222–224, 226</td>
</tr>
<tr>
<td>Venegas, Father Alonso Messia</td>
<td>24</td>
</tr>
<tr>
<td>Victoria (queen of England)</td>
<td>39, 55</td>
</tr>
<tr>
<td>Victoria Falls</td>
<td>36</td>
</tr>
<tr>
<td>Vietnam War</td>
<td>chloroquine resistance in, 248–249</td>
</tr>
<tr>
<td>mefloquine in</td>
<td>137–146</td>
</tr>
<tr>
<td>qinghaosu in</td>
<td>171</td>
</tr>
<tr>
<td>tafenoquine in</td>
<td>133–134</td>
</tr>
<tr>
<td>Vinccke, Ignace</td>
<td>221</td>
</tr>
<tr>
<td>von Baeyer, Adolf</td>
<td>210</td>
</tr>
<tr>
<td>von Humboldt, Alexander</td>
<td>53</td>
</tr>
<tr>
<td>von Liebig, Justus</td>
<td>53, 55</td>
</tr>
</tbody>
</table>

Universities Mission to the Shire Highlands, 37
Index

W
Wagner-Jauregg, Julius, 65–66
Waksman, Selman, 191–193
Walcheren, Holland, military encampment, 56
Waldeyer, Wilhelm, 59
Walpole, Horace, 3
Walsh, Charles, 108, 182–183
Walter Reed Army Institute of Research
antimalarial drug screening by, 248–249
artemisinin work of, 170, 173, 175
malaria drug development program of, 133
malaria pigment research at, 164–166
mefloquine development in, 138–140, 144–146
vaccine development by, 230–235
Walter Reed General Hospital, 144
Warhurst, David, 164–165
Wartime, malaria significance in, 171
American Revolution, 43–48
Civil War, 44–45
Korean War, 129–133
Vietnam War, see Vietnam War
Walcheren encampment, 56
World War II, see World War II
Washington, General George, malaria as ally of, 46–48
Water, mosquito breeding in, see Wetlands and mosquito breeding sites
Waterproofing, coal tar for, 54
Watson, James, 153
Wei, Zhenxing, 171
Weigert, Carl, 59
Weigert, Rosa, 59
Weinberg, Arthur, 62
Welch, William Henry, 7, 9
Wellcome, Sir Henry, 94
Wellcome Research Laboratories
atovaquone development by, 110, 113, 116–117
proguanil development by, 107
Wellems, Thomas, 166–167
Wenyon, C. M., 96–97
Wernersdorfer, Walther, 168
Wetlands and mosquito breeding sites
in American Revolution, 47
bonification of, in Italy, 48–50
early awareness of, 3–4
in England, 25–26
mosquito control in, see Mosquito control
at Walcheren, Holland, 56
Wilhelmina (queen of The Netherlands), 160
Wilkins, Maurice, 153
Williamson, Don, 183–184
Wilson, Iain, 183–184
Wingler, August, 122
Winthrop Chemical Corporation, 69–70, 77, 79
Wirth, Dyann, 167
Wiselogle, Frederick Y., 126
Woods, Donald, 89–90
Woodward, Robert, 159–160, 194
Works Progress Administration, mosquito control program of, 45
World Health Assembly, 212–213, 241–242
World Health Organization
Chemotherapy of Malaria Steering Committee, 140–141, 145–146, 168–170
on eradication, 240
eradication programs of, 213, 246
Global Eradication Program of, 80
Global Malaria Eradication Campaign of, 150
malaria pigment research of, 164–165
Special Programme for Research and Training in Tropical Diseases, 117, 140, 145, 148, 168–170
World Health Assembly of 1956, 150
World War I, streptococcal infections in, 84

World War II
Atabrine in, 69–76, 126
bed nets used in, 239
bird malaria studies during, 221
chloroquine in, 76–80
cinchona trees, unavailability due to, 70
DDT use in, 210–212
drugs developed during, 249–250
dydroxynaphthoquinones in, 112
pamaquine in, 122, 126, 129–130
parasites identified in liver, 19–20
penicillin discovery in, 188–191
proguanil in, 104–105
quinine shortage in, 159–160
sulfonamide in, 91

Wormwood, see Artemisia annua;
Artemisinin (qinghaosu)

WR-30090, 144
WR-33063, 144

WR-99210, 162, 163
WR-142490, 140, 144, 248–249, see also Mefloquine
WR-225448 (aminoquinoline), 133–134
WR-238605 (aminoquinoline), 134
Wrigglesworth, Roger, 113–114

Y
Yellow fever, 32
in Brazil, 209
in India, 209
in Panama Canal construction, 40–42
Yoeli, Meir, 222
Yorke, Warrington, 104

Z
Zambezi River, exploration of, 37
Zeidler, Othmar, 210
Zygotes, proteins of, 214, 216