THE
ELUSIVE
MALARIA VACCINE
MIRACLE OR MIRAGE?
THE
ELUSIVE
MALARIA VACCINE
MIRACLE OR MIRAGE?

IRWIN W. SHERMAN

Department of Biology
University of California
Riverside, California

Department of Cell Biology
Institute for Childhood and Neglected Diseases
The Scripps Research Institute
La Jolla, California

ASM PRESS
Washington, DC
In the hope that the children of the world will no longer face the scourge of malaria, I dedicate this book to my grandchildren, Zachary, Jack, and Nathaniel.
# Contents

Preface ix

1 Hunting Microbes 1
2 Malaria, the Sickness 42
3 The Immunity Alphabet 49
4 From Milkmaids to Vaccines 76
5 Fundamental Findings 90
6 Dreams about Vaccines 111
7 Promises, Promises, Promises 131
8 Hunting for Protective Blood Stage Antigens 158
9 Blocking Transmission 188
10 Battling Blood Stages 216
11 Of Mice and Men 234
12 Informed by the Immune System 284
13 Why the Vaccine Remains Elusive 319

References 327
Index 375
Cats may be killed by curiosity, but science dies for the lack of it.
G. G. Simpson

Preface

Malaria is one of humankind’s greatest killers. In sub-Saharan Africa, every 30 s a child, usually under 5 years of age, dies from malaria. The disease afflicts 300 million to 500 million people, and 36% of the world’s population, in more than 90 countries and territories, is still exposed to the risk of malaria. If the global population continues to grow as expected, almost 3.5 billion people will be living in areas affected by malaria by 2010. Although most people in Asia and the Americas now live in areas where the risk of malaria is low, serious problems remain in economically underdeveloped areas and countries affected by social disruption. Of great concern is that a surge of malaria infections is occurring in places previously free of the disease. Over the years, the malaria parasite, *Plasmodium*, has become resistant to a variety of medicines, and often the best medicines are either not available or too expensive for millions of people in developing nations. Further exacerbating the problem is the combination of insecticide resistance in the mosquitoes that transmit the parasite and economic constraints. Some scientists believe that a vaccine is our only hope to eradicate the disease.

The hunt for a malaria vaccine has been unfolding for a century. It has been punctuated by periods of intense activity and excitement followed by inaction and boredom. The quest has been enlivened by controversy; there have been wars of words, and errors have been made, sometimes honest but sometimes not. Ideas have been stolen, credit for discovery has gone unacknowledged, and there have been and continue...
to be intense rivalries with clashes of ego and even scandals. This book chronicles all these aspects of the hunt for a malaria vaccine. It tells of the slow and erratic research, the promises of success and the disappointing failures, and the fierce competition between the microbe hunters who have had as their single goal a protective malaria vaccine able to reduce morbidity and mortality by one of the world’s most notorious assassins.
Index

Acquired immunity, 61, 66, 69, 74, 95–96, 171
  naturally acquired, 291–301
  slow onset of, 292–293
ACT, see Artemisinin-based combination treatment
Active immunization, 54
Adams, John, 281
Adenovirus vector, 263
Adjuvant 65, 124
Adler, Saul, 124
Aestivo-autumnal malaria, 18
Africa, European colonial expansion, 12–13
African Americans, resistance to malaria, 289
African sleeping sickness, 107, 114
Ague, 2, 47
AIBS, see American Institute of Biological Sciences
Albumin, 56
Alexander the Great, 47
Allee, W. C., 311
Allison, A. C., 296
Alonso, Pedro, 258–259
Alpers, Michael, 166
Alpha globulin, 56
Altruistic vaccine, see Transmission-blocking vaccine
Alum, 67, 256–257
Aluminum hydroxide, 67
Alving, Alf, 306
Alving, Carl, 306
AMA-1 (apical membrane antigen), 129, 169, 181–184, 229, 260, 262–263
AMA-1 gene, 182–183
polymorphism, 183–184
American colonies, 10, 47
American Institute of Biological Sciences (AIBS), 150–151
Amgov, Evelina, 310
Amodiaquine, 45
Amyloid P protein, serum, 69
Anders, Robin, 166–167, 182
Anderson, C. R., 19
Anemia, severe malarial, 42–43, 69, 279, 298
Aniline dyes, 17, 52
Animal models, 91, 131–139, 294
Animalcules, 3, 9–20
Anopheles, 23, 31–32, 36, 133, 188
Anopheles gambiae, 36, 195–196
Anopheles stephensi, 36
Anthrax, 6–7, 81, 84–85
Anthrax vaccine, 82–86
Antibody(ies), 49–57, 104, 161, 293,  
see also Immunoglobulin  
antigen-antibody interactions, 55–56, 58  
maternal, 302  
parasite-killing, 96  
production, 162  
protective, 123, 172  
synthesis and secretion, 70–72  
Antibody titer, 53, 110  
Antibody-dependent cellular inhibition, 276  
Antibody-dependent cellular toxicity, 60  
Antidisease vaccine, 278–280  
Antigamete immunity, 205–207  
Antigametocyte immunity, 202  
Antigen(s), 55  
antigen-antibody interactions, 55–56, 58  
malarial components, 99–100  
protective, 102–103  
purification, 164  
Antigenic determinant, 56, 58, 107, 162–163  
Antimalarial drugs, 44–46, 193, 197–198, 320, see also Drug resistance; specific drugs  
costs, 46  
drug development, 46  
drug testing, 131  
screening drug candidates, 92  
search for new drugs, 131, 302  
for transmission control, 198–199  
Antiserum, 51  
Antisporozoite antibodies, 251–255  
Antitoxicity vaccine, 278–280  
Antitoxin, 51, 53–55, 68  
Aotus monkeys, 141–142, 144, 150–151, 153, 158, 185, 227  
Apical membrane antigen, see AMA-1  
Artemether, 45  
Artemisinin, 45, 320  
Artemisinin-based combination treatment (ACT), 45–46  
Artemotil, 45  
Artesunate, 45  
AS01, 277, 306  
AS02, 184, 277  
AS02A, 177, 310  
Asexual-stage antigens, 184–187  
Asia Pacific Conference on Malaria (1985), 152–153  
Atkinson, 19  
Atovaquone, 45–46  
ATS domain, 219  
Attenuated strain, 81–86, 95, 108–109, 126, 160  
Attenuation, 321  
by gene knockout, 280–283  
by irradiation, 234–251  
Avery, Oswald, 108  
Azo dyes, sulfonamide-containing, 107  
B cells, 67, 70–75, 97–98, 161–162, 223, 294  
B cell-deficient birds, 97–98  
Babesia rodhaini, 118–119  
Bacillus Calmette-Guérin (BCG), 87–88, 297  
Bacillus malariae, 13–14, 16  
Bacterial vaccine, 88–89  
Bacteriophage λ, engineered, 165  
Bacteriophage λgt11, 168  
Ball, Eric, 135  
Ballou, Ripley, 186–187, 256, 258–259, 267  
Band 3 protein, 316–318  
Bannister, Lawrence, 123  
Barbarossa, Frederick, 47  
Barnwell, J. W., 121  
Bass, C. C., 137
Index

Bastianelli, Giuseppe, 30, 32, 35, 216
BCG, see Bacillus Calmette-Guérin
Beale, Geoffrey, 166, 200
Beaudoin, Richard L., 261, 270–271, 275–276
Becker, Elmer, 304
Bed nets, 190, 198, 214
insecticide-impregnated, 36–37, 214–215, 320
Benacerraf, Baruj, 253
Benenson, Abraham, 304
Ben-Harel, Shulamite, 91
Berenbaum, Morris, 115
Beta globulin, 97
Bier, Otto, 253
Bignami, Amico, 18, 28, 30, 32, 35, 216
Bill and Melinda Gates Foundation, 66, 222, 258, 268, 320, 322
Biological warfare, 84–85
Biomedical Primate Research Centre, 183
Biothrax, 85
Birds, see Avian malaria
Bishop, Ann, 201
Biswa, P., 106
Black howler monkeys, 132
Blackman, M. J., 176
Blood, 59
Blood films, stained, 43–44
Blood flukes, 241
Blood group O, 224
Blood stage antigens, 158–187, 309
Blood stage malaria, 216–233, 293–298
Bloom, W., 38
Bone marrow, 70, 72
Booster shot, 71
Bordet, Jules, 67–69
Borneo fireback pheasant, 92
Bouley, Henri, 82
Boyd, George, 91
Boyd, Mark F., 288–289
Bray, R. S., 250
Brown, Graham, 166–167
Brown, Harold, 228
Brown, Ivor, 115–116, 118, 217
Brown, Neil, 114–116, 118–121, 123, 128, 130, 134, 217
Brumpt, Emile, 91–92
Bueding, Ernest, 314
Bujard, Hermann, 310
Burns, Jim, 178
Bursa of Fabricius, 70, 97
bursaless birds, 97–98
Butcher, Geoffrey, 117, 122–123, 227
Calmette, Albert, 87–88, 94
Camus, David, 230, 307
Canal Zone, 190
Canary model, 91, 234–235
Candle jar, 138–139
Canfield, Craig, 229
Cannon, P. R., 221
Carter, Henry VanDyke, 18
Carter, Richard, 200–207
Caventou, Joseph, 12, 45
CD36 molecule, 222, 224, 317
cDNA library, 165–168, 281, 308
Celli, Angelo, 16–17
Cell-mediated immunity, 72–75, 294–298, 324–325
Cerebral malaria, 43, 65, 219–220, 265, 295, 298
Chamberland, Charles-Édouard, 83, 85
Chemokines, 60, 279
Chemotherapy, 55
Chen, David, 205–206
Chicken, domestic, 92
Childbed fever, 5–6
Childhood immunization, 319–320
Chloroquine, 37, 45–46, 98, 112, 275, 277
Chloroquine resistance, 45–46, 131, 302
Chlorproguanil, 46
Cholera, 68, 81
Cholera toxin, 213
Cholera vaccine, 81–82
Chondroitin sulfate A (CSA), 222–223
Christophers, Sir Rickard, 189
CIDR domain, 219–220, 224
Cinchona alkaloids, 12
cir gene family, 119
Circulatory system, 59–60
Circumsporozoite precipitation (CSP) reaction, 243, 247
engineered, 308
Civil War, 47
Clark, Ian A., 174, 297
Cleveland, L. R., 302
Clinical presentation of malaria, 10–11, 42–48
Clone, 162
Clostridium tetani, 50
Clyde, David, 245–248, 250–251, 266
Coggeshall, Lowell, 92, 106, 108
Cohen, Joe, 257
Cohn, Ferdinand, 7
Complement, 67–69, 74
alternative pathway of activation, 69
classical pathway of activation, 69
Complement fixation, 69
Conquistadors, 9–10
Conspiracy, 146–157
Coombs, Robin, 118
Coppel, Ross, 167–168
Cor, George, 172–176
Cross-reaction, immunological, 58, 108
Cross-reactive antibodies, 293
CS gene, 252–255, 307–308
CSA, see Chondroitin sulfate A
CSP, see Circumsporozoite protein
CSP reaction, see Circumsporozoite precipitation reaction
CSP vaccine, 254–261, 267
CTL, see Cytotoxic T lymphocytes
Cuboni, Giuseppe, 13
Culture medium, 138
spent medium, 307
liver stages, 277
Cysteine-rich proteins, 169
Cytokines, 60, 63–64, 66, 73–75, 279, 294–295, 298
Cytotoxic T lymphocytes (CTL), 60, 72–74, 261–262
D’Alesandro, Philip, 314
Daly, Tom, 179
Dame, John, 308
Danilewsky, Basil, 90
D’Antonio, Lawrence, 127–128
Dapsone, 46
Das Gupta, B. M., 105
Davis, Ronald, 168
DBL (Duffy ligand binding) domain, 219, 224
DBP, see Duffy-binding proteins
DBR, see DIDA-binding region
DDT, 37, 111, 196–198
DDT resistance, 37
de Lesseps, Ferdinand, 189
Dead vaccine, 83
Deans, Judith, 129, 181–182
Death rate, 47–48
Dendritic cells, 61–63, 66–67, 73–75, 121, 298
Dennis, Dave, 123, 182
Dense granules, 226
Desowitz, Robert, 221, 228–229, 249–250
Devaine, Casimir-Joseph, 6
Dexamethasone, 265
Diagnosis of malaria, 43–44
Diaz, George, 151
Dichloro-diphenyl-trichloromethane, 196
DIDA, 317
DIDA-binding region (DBR), 317–318
Dideoxy sequencing, 170–171
Diggs, Carter, 145, 156, 303–311
Dionisi, Antonio, 30
Diphtheria, 49–51, 53–55, 71
Diphtheria toxin, 50, 53, 55, 88
Disulfide bonds, 209
DNA sequencing, 166, 170
DNA vaccine, 88, 155, 157, 213, 220, 261–263, 300, 324
Dochez, Alphonse R., 108
Domagk, Gerhard, 107
Doolan, Denise, 299–301, 311
DPT vaccine, 55, 71, 89, 321
Drug resistance, 45–46, 237–238
Druilhe, Pierre, 267, 276–277
Duffy, P. E., 222
Duffy blood group, 227–231, 250–251, 289
Duffy-binding proteins (DBP), 230–231
Easmon, Charles, 116
Eaton, Monroe, 106, 115–116, 217
EBA, see Erythrocyte-binding antigens
Ebers Papyrus, 9
Ehrlich, Paul, 16–17, 51–55, 114, 286–287
Electrophoresis, 57
serum proteins, 56
Ellis, Joan, 254
Embezzlement, 153
Emperor effect, 157
Enders, J., 159–160
Entzeroth, Rolf, 281
Enzyme heterogeneity, 314
Enzyme stripping, 227–228
Epitope, 56, 58, see also Antigenic determinant
cryptic, 293
Epstein, J.E., 260, 264
Erickson, James M., 147–151, 154–155
Erythrocyte(s), irradiated, 143
Erythrocyte-binding antigens (EBA), 169
EBA-175, 230
Erythrocytic schizogony, 41
Espinal, Carlos, 150
Eugui, E.M., 296
European explorers, 9–10, 12–13
Exflagellation, 19, 40, 201–202
“Exoantigens,” 306–307
Exoerythrocytic forms, 37–41, 268–278
immunological responsiveness, 103–105
Expression library, 165
Eyles, Don E., 202
Fab fragment, 57–58
Fairley, Neil, 38
Fansidar, 46
Fansimef, 46
Farley, Patrick, 179
Fauci, Anthony, 179
Fc fragment, 57–58
Fedchenko, Alexei, 22
Fermentations, 3–4
Fertilization, 209
Fertilization-preventing antibodies, 207
Fincham, John, 175
Finerty, John, 98
Flow vial culture system, 137–139
FMP0111 protein, 277
FMP-1, see MSP-1
FMP2.1/ASO2A vaccine, 184
Fowlpox virus vector, 262
FP9-MVA-TRAP, 263
Fracastoro, Girolamo, 285–286
Fraud, 147–157
Freeman, Robert, 174, 176
Freund, Jules, 100–102, 109–110, 117
Freund’s adjuvant, 103, 309–310
Freund’s complete adjuvant, 109–110, 117, 128, 144–145, 152, 154, 219–220, 238
Freund’s incomplete adjuvant, 117, 144
Fried, Michal, 221–222
Friedl, Frank, 312–313
Friedman, Milton, 139
FSV-1 vaccine, 256, 267, 308
FSV-2 vaccine, 256
Fulton, J. D., 110
Fumigating smoke, 194
Gamete(s), antibodies against, 199–215
Gamete surface antigens, 209–213
Gametocytes, 19, 40–41
suspended animation medium, 201
test tube manipulations, 200–201
transmission-blocking vaccines, 199–215
Gamma globulin, 56, 97, 110, 112–113, 161, 301–302
Garnham, P. C. C. (Cyril), 38–39, 122, 204
Geiman, Quentin M., 133–136
Gene(s), isolation, 164
Gene knockouts, 121, 280–283
Genetic cross, P. falciparum, 200, 202
Genomic library, 165–166, 308
Gerhardt, Carl, 16
Gerrick International, 151
Giemsma, Gustav, 44, 194
Giemsma stain, 44
Gingrich, Wendell, 99
Glick, Bruce, 70
Global Malaria Eradication Program (WHO), 111, 124
Globulin, 56–58
Glycerinated calf’s lymph, 79
Glycosylphosphatidylinositol moiety, 63–64, 176–177, 279–280
Glynn, Alan, 116
Godson, Nigel, 254
Goldstein, F., 96
Golgi, Camillo, 17–18, 278
Good, Michael, 232, 300
Goodwin, Len, 237
Gordon, Daniel, 256
Gorgas, William C., 132, 190
Gorgas Memorial Laboratory, 132–134
Grabar, Pierre, 252
Graham, Harry, 271
Granulocytes, 59
Granzymes, 63, 75
Grassi, Giovanni Battista, 37
rivalry with Ross, 26–37
Greenwood, Brian, 65–66
Grun, Jim, 297
Guérin, Camille, 88
Gwadz, Robert, 201–206, 253–254
Hackett, Lewis H., 191, 279
Hadley, Terence, 230, 307
Haemoproteus, 19
Halofantrine, 45–46
Halofantrine resistance, 46
Hand washing, 6
Hanging drop method, 7
Harrington, Sir Charles, 115
Hartman, Ernest, 91
Hawking, Frank, 115, 119
Haynes, David, 306, 308
Heat-shock proteins, 142
Hegner, Robert W., 91
Heidelberger, Michael, 107–109, 232, 301, 305
Heligmosomoides polygyrus, 298
Hellyer, Tobin, 116
Hematozoa of Malariae (Osler), 18
Hemichrome, 317–318
Hemolysis, 68–69
Hemozoin, see Malaria pigment
Henry the Navigator, 9–10
Hepatitis B virus vaccine, 321
Heppner, Gray, 256–258, 260
Herd immunity, 199, 215
Herrera, Socrates, 185
Hewitt, Reginald, 91
Hill, Adrian, 263
Hippocrates, 9
Histidine-rich protein (HRP), 103
Historical impact of malaria, 47–48
Hockmeyer, Wayne, 307–308
Hoffman, Erich, 286
Hoffman, Stephen L., 256, 261, 264–268, 281, 300
Hogness, David S., 167
Holbrook, Thomas, 271
Holder, Anthony, 174–176, 178–179
Hollingdale, Michael, 155, 270
Holmes, Oliver Wendell, 5
Holofernes (Assyrian General), 214
Hookworm disease, 191
Hopkins, Johns, 19
Howard, James, 173
Howard, Lee, 124
Howard, Randall, 142
HPLQKTY (amino acid sequence), 316–317
HRP, see Histidine-rich protein
Huff, Clay, 38, 91, 133, 202, 205, 261, 268–270
Hull, Robert, 312
Humoral immunity, 71, 74
Hybridoma, 163–164
Hypnozoites, 39, 43

Immunization, 54
Immunofluorescence microscopy, 174
Immunoglobulin, 56–57, see also Antibody(ies)
structure, 57–58
Immunoglobulin A, 57–58
Immunoglobulin D, 57
Immunoglobulin E, 57–58
IgG1, 276
IgG3, 276
Immunoglobulin M, 57–58, 69, 106, 123, 223–224
Immunosense, 301
Immunotherapy, 68
Indian junglefowl model, 92
Inflammation, 61
Influenza vaccine, 89, 321
Influenza virus vector, 263
Informed consent, 289
Innate immunity, see Natural immunity
Inouye, Daniel K., 153
Insect repellents, 36, 198
Insecticide(s), 37, 111–112, 191, 194, 196, 214–215, 320
Insecticide resistance, 197
Interferon gamma, 61–67, 74–75, 253, 261–262, 272, 275, 295, 299
Interleukin(s), 60, 62
Interleukin-1, 63, 279
Interleukin-2, 65
Interleukin-4, 261, 272
Interleukin-5, 261
Interleukin-6, 63, 261, 279
Interleukin-8, 63–65, 295
Interleukin-10, 75, 261
Interleukin-12, 63–67, 74–75, 261, 294–295
Interleukin-18, 63
Intermittent fever, 2–3
International Insect Research and Development (IIRD), 149
Interstitial fluid, 59
Irradiation, attenuation by, 234–251
Irrigation ditches, 188–189
Jacobs, Walter, 107
James, Sydney Price, 38, 189, 287
Japanese encephalitis vaccine, 88
Jeake, Samuel, 2
Jenner, Edward, 78–79, 232
Jennerian technique, 78–79
Jesty, Benjamin, 78
Johns, F. M., 137
Johns Hopkins School of Hygiene and Public Health, 91–93
Johnson, Carl, 132–133
Joint Malaria Programme, 66
Jordan, Dorothy, 154
Juhl, J., 104
Kabat, Elvin, 56, 252–253
Kaplan, Nathan, 206, 314
Kappe, Stefan, 280–283
Karush, Fred, 178
Kaslow, David C., 211–213, 221
Kellerman, Gottfried, 148–149
Kelsch, L. F. Achille, 14–15
Kemp, David, 167
Kidd, Fred, 179
Kimmel, Araxie, 102–103, 141
Kill, J. A., 82
Killick-Kendrick, Robert, 204
Kitasato, Shibasaburo, 50–51, 278
Klebs, Edwin, 13, 50
Klots, Alexander, 241
Klotz, Irving, 313
Knobs, 217, 229, 315–317
Knowles, Robert, 105
Koch, Hedwig, 291
Koch, Robert, 3, 6–7, 31–32, 36, 50, 52, 68, 81, 83, 100–101, 278, 281
rivalry with Pasteur, 8–9
Koch’s postulates, 7–8, 13
Köhler, Georges, 162–163
Kolletschka, Jakob, 5
Korean War, 47, 311
Kra monkeys, 105, 227
KT&R Laboratories, 149
Kudo, Richard, 133
Kumm, H., 108
LA-15-PH, 154
Lackey, James B., 311
Lactate dehydrogenase, 314
Lancisi, Giovanni, 14
Landsteiner, Karl, 107–108
Landy, Maurice, 98
Langhorne, Jean, 121
Langreth, Susan, 140–141, 155, 161
LAPDAP, 46
Lapudrine, 46
Larvicides, 36–37, 189, 191, 195, 198
Latent infection, 94
Laveran, Charles-Louis Alphonse, 9–20, 33, 35, 90
Leishman, W. B., 44
LePage, Dick, 118
Leprosy, 116
Leukocytes, 59
Life cycle, Plasmodium, 37–41, 90–110
Ling, Irene, 176
Lips, Marcel, 242
Liver, dysfunction in malaria, 42
Liver stage antigens (LSA), 268–278, 282–283
LSA-1, 276–277, 299
LSA-3, 277–278, 299
Liver stage malaria, 298–299
Liver stage vaccine, 268–278, 282–283, 324
Lock-and-key theory, 55–56
Loeffler, Friedrich, 50
Long, Carole, 176, 178–180
Longenecker, B., 97
Lorand, Lazlo, 313
Loucq, Christian, 260, 268
LSA, see Liver stage antigens
Luke, T. C., 264
Lumefantrine, 46
Lyanga, John J., 296
Lymph, 60
Lymph nodes, 60, 70, 72, 271
<table>
<thead>
<tr>
<th>Term</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic system</td>
<td>59</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>59–61, 63</td>
</tr>
<tr>
<td>Lyon, Jeffrey</td>
<td>182, 310</td>
</tr>
<tr>
<td>MacCallum, William</td>
<td>19–20, 100</td>
</tr>
<tr>
<td>MacDonald, George</td>
<td>191–193</td>
</tr>
<tr>
<td>Mackaness, George</td>
<td>297</td>
</tr>
<tr>
<td>Macrogametes</td>
<td>41</td>
</tr>
<tr>
<td>Macroglobulin, see Immunoglobulin M</td>
<td></td>
</tr>
<tr>
<td>Macrophages</td>
<td>60–63, 72, 74–75, 223, 279, 295–297</td>
</tr>
<tr>
<td>Maegraith, Brian</td>
<td>278–279</td>
</tr>
<tr>
<td>Majarian, Will</td>
<td>178</td>
</tr>
<tr>
<td>Major histocompatibility complex (MHC)</td>
<td>72</td>
</tr>
<tr>
<td>MHC I, 72, 74</td>
<td></td>
</tr>
<tr>
<td>MHC II, 72</td>
<td></td>
</tr>
<tr>
<td>Mal’aria</td>
<td>9</td>
</tr>
<tr>
<td>Malaria Centre</td>
<td>66</td>
</tr>
<tr>
<td>Malaria eradication</td>
<td>37, 45, 111, 131, 189–191, 196–198, 236, 320</td>
</tr>
<tr>
<td>Malaria genes, cloning</td>
<td>167</td>
</tr>
<tr>
<td>Malaria Immunology and Vaccine Research Program, see MIVR</td>
<td></td>
</tr>
<tr>
<td>Malaria pigment</td>
<td>14–17, 21, 29, 41–42, 61, 63, 67, 75, 313</td>
</tr>
<tr>
<td>Malaria prevention</td>
<td>36</td>
</tr>
<tr>
<td>Malaria toxin</td>
<td>278–279</td>
</tr>
<tr>
<td>Malaria Vaccine Development Program (MVDP)</td>
<td>157</td>
</tr>
<tr>
<td>Malaria Vaccine Initiative (MVI)</td>
<td>258</td>
</tr>
<tr>
<td>The Malaria Vaccine Technology Roadmap</td>
<td>325–326</td>
</tr>
<tr>
<td>Malaria therapy</td>
<td>38, 105, 246, 285–291, 293</td>
</tr>
<tr>
<td>Malarone</td>
<td>45–46</td>
</tr>
<tr>
<td>Malefeasance</td>
<td>146–157</td>
</tr>
<tr>
<td>Malignant malaria</td>
<td>18</td>
</tr>
<tr>
<td>Maloprim</td>
<td>46</td>
</tr>
<tr>
<td>Malstat</td>
<td>314</td>
</tr>
<tr>
<td>Manson, Patrick</td>
<td>14, 21–22, 26, 28–29, 33, 35, 214</td>
</tr>
<tr>
<td>Manson, Thurburn</td>
<td>35, 39</td>
</tr>
<tr>
<td>Manwell, Reginald</td>
<td>91, 96</td>
</tr>
<tr>
<td>Marchiafava, Ettore</td>
<td>13, 16–18</td>
</tr>
<tr>
<td>Margolis, George</td>
<td>304</td>
</tr>
<tr>
<td>Marmur, Julius</td>
<td>314</td>
</tr>
<tr>
<td>Marston, Robert</td>
<td>303</td>
</tr>
<tr>
<td>Master-apprentice relationship</td>
<td>33–36</td>
</tr>
<tr>
<td>Maternal antibodies</td>
<td>302</td>
</tr>
<tr>
<td>Matuschewski, Kai</td>
<td>281–282</td>
</tr>
<tr>
<td>Mauvais, Père</td>
<td>277</td>
</tr>
<tr>
<td>Mayer, Manfred</td>
<td>108</td>
</tr>
<tr>
<td>Mazza, S.</td>
<td>94</td>
</tr>
<tr>
<td>McBride, Jana</td>
<td>176</td>
</tr>
<tr>
<td>McCarthy, Joseph</td>
<td>125</td>
</tr>
<tr>
<td>McCutchan, Tom</td>
<td>308</td>
</tr>
<tr>
<td>McDonald, Vincent</td>
<td>103</td>
</tr>
<tr>
<td>McGhee, Barclay</td>
<td>226</td>
</tr>
<tr>
<td>McGregor, Ian</td>
<td>111–113, 122, 242, 301, 319</td>
</tr>
<tr>
<td>MDP (muramyl dipeptide)</td>
<td>141–142, 144–145</td>
</tr>
<tr>
<td>B30-MDP, 154</td>
<td></td>
</tr>
<tr>
<td>stearoyl-MDP, 145</td>
<td></td>
</tr>
<tr>
<td>Measles vaccine</td>
<td>88</td>
</tr>
<tr>
<td>Meckel, Heinrich</td>
<td>15</td>
</tr>
<tr>
<td>Medawar, Sir Peter</td>
<td>118–119</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>45–46, 302</td>
</tr>
<tr>
<td>Mefloquine resistance</td>
<td>46</td>
</tr>
<tr>
<td>Meister, Joseph</td>
<td>86–87</td>
</tr>
<tr>
<td>Meltzer, Monte S.</td>
<td>295</td>
</tr>
<tr>
<td>Memory cells</td>
<td>71, 74</td>
</tr>
<tr>
<td>Ménard, Robert</td>
<td>281</td>
</tr>
<tr>
<td>Merozoite(s)</td>
<td>40–42, 94, 103, 123, 271</td>
</tr>
<tr>
<td>invasion of red cells</td>
<td>171–182, 225–231, 293, 324</td>
</tr>
<tr>
<td>invasion of reticulocytes</td>
<td>231</td>
</tr>
<tr>
<td>Merozoite antigens</td>
<td>123, 141, 169, 171</td>
</tr>
<tr>
<td>Merozoite surface antigens</td>
<td>142, 168</td>
</tr>
<tr>
<td>Merozoite surface protein(s)</td>
<td>157, 169</td>
</tr>
<tr>
<td>Merozoite surface protein 1, see</td>
<td></td>
</tr>
<tr>
<td>MSP-1</td>
<td></td>
</tr>
<tr>
<td>Merrifield, Bruce</td>
<td>185</td>
</tr>
<tr>
<td>Metchnikoff, Elie</td>
<td>19, 61–62, 68</td>
</tr>
<tr>
<td>Methylened blue</td>
<td>17</td>
</tr>
<tr>
<td>Methylened blue and eosin</td>
<td>43</td>
</tr>
<tr>
<td>MF59, 219–220</td>
<td></td>
</tr>
<tr>
<td>Miasma</td>
<td>3–4, 13</td>
</tr>
</tbody>
</table>
Miasmatic fever, 2
Microbe hunters, 2–9
Microbial immunology, 273–274
Microfilariae, 21–22
Microgamete(s), 41
Microgamete immobilization reaction, 204
Micronemes, 226
Microorganisms, discovery, 1–41
Miller, Jacques, 167–168, 173
Milstein, César, 162–163
Mitchell, Graham, 123, 143, 166–168, 227
MIVR (Malaria Immunology and Vaccine Research program), 146–157
Molecular biology, 166
Molecular photocopying, 169–170
Monkey(s), acquisition/purchase/housing, 149–151
Monkey malaria, 39, 105–110, 131–139, 245, 323
CSP, 307
protective, 172
to sporozoite antigen, 252
Monocytes, 59, 62, 64, 67, 75
Monophosphoryl lipid A, 255
Montanide, 183, 277
Morado, 19
Mosquito
blood-feeding habits, 191
distance flown to take blood meal, 193
human-biting habits, 193
injection of irradiated sporozoites by, 246–249
insecticide resistant, 197
life expectancy of female after blood meal, 193
maturation period, 193
transmission of malaria, 20–26, 28–29, 31–32, 35–36
transmission-blocking vaccines, 188–215
Mosquito breeding grounds, 189–190, 193–194, 198
Mosquito control, 36–37, 111, 188–199
“Mosquito Day,” 29
Mosquito inspectors, 194
Mosquito nets, see Bed nets
Mosquito stage vaccine, 199–215
Most, Harry, 242–244, 248, 253
genetic aspects, 296–297
MPL, 256–258
mRNA, 165, 168
MSP-1 (merozoite surface protein 1), 171–181, 229, 260, 263, 309–311
binding to red cells, 177
MSP-119, 176–177, 179
MSP-142, 177, 262
MSP-1 gene, 176–177
polymorphisms, 310
processing, 177
sequence analysis, 177
MSP-3 (merozoite surface protein 3), 276
Mueller, A. K., 282
Müller, Paul, 196
Mulligan, H. W., 105, 235, 239
Multiplier of the disease, 192–193
Muramyl dipeptide, see MDP
MuStDo program, 262
MVI, see Malaria Vaccine Initiative
MVDP, see Malaria Vaccine Development Program
Myeloma, 162
Nair, C., 105
NANP protein, 255
Nasal vaccination, 213
National Impregnated Bednet Programme, 215
National Institute for Medical
Index

Research (NIMR), 114–116, 119–121
Natural immunity, 61–69, 74
Natural killer (NK) cells, 60–61, 63–64, 66, 74–75, 295, 298
Naturally acquired immunity, 291–301
Neal, Ralph, 240
Nei Ching (Chinese medical text), 9
Nelms, Sarah, 78
Neutrophils, 61, 74
Newbold, Chris, 118
Newborn infants, 112
Nicolaier, Arthur, 50
Night owl monkeys, 133–135
Nijhout, Mary, 201
NIMR, see National Institute for Medical Research
Nitric oxide, 75, 209, 275, 280, 299
NK cells, see Natural killer cells
Nobel Prize
Behring, 54
Domagk, 107
Köhler and Milstein, 163
Medawar, 118
Metchnikoff, 62
Ross, 32, 34–35
Sanger, 166
Wagner-Jauregg, 287
Weller, 160
Nocht, Bernard, 44
Noguchi, Hideyo, 286
Nonhuman primate malaria, 39–40, 131–139, 183, 323
“Nonself,” 59
Nussenzweig, Victor, 252–254, 272, 281
Nwuba, Roseangela, 176
NYVAC-Pf7 vaccine, 184, 211
Ogun, Solia, 176
Omer, Fakhreldin, 65
Oocysts, 24–26, 37, 40–41
Ookinete(s), 19–20, 25, 41
antibodies against, 199–215
formation, 207
monoclonal antibodies against, 210
Ookinete surface antigens, 210–211
Opie, Eugene, 19, 100
Opsonization, 71, 75
OptiMal, 314
Oscillaria, 17
Oscillaria malariae, 15
Osler, Abraham, 305
Osler, William, 18–19
Ovary, Zoltan, 253
Owl monkeys, 132–133, 136–137, 143, 145, 149–151
Paludisme, 2–3, 13
Pamaquine, 91
PAMP, see Pathogen-associated molecular patterns
Panama Canal, 189–190
Paper electrophoresis, 57
Paris green, 191, 195
Paroxysms, 42
Passive immunity, 51
Passive immunization, 51, 54, 113
Passive-transfer study, 302
Pasteur, Louis, 3–5, 68, 80–87, 94, 232, 234
rivalry with Koch, 8–9
Pasteur Institute, 84
colonial, 94
Patarroyo, Manuel Elkin, 184–186
Patents, 127, 164, 254, 282, 301
Pathogen(s), discovery of microorganisms, 1–41
Pathogen-associated molecular patterns (PAMP), 62–63
Pathogenesis of malaria, 42–48
PCR technique, 169–170
Pébrine disease, 4–5
Pelletier, Pierre, 12, 45
Perforin, 63, 75
Permin, A., 104
Peruvian Primatological Project, 150
Petri, Julius, 138
Petri dish culture, 158
Pf195, see MSP-1
Pfalhesin, 317–318
Pfeiffer, Richard, 68
PiEMP1 (P. falciparum erythrocyte membrane protein), 169, 218–
219, 222–223, 292–293
adhesive domains, 219
vaccine based on, 219–220
Pfs25 gene, 211
Pfs25 protein, 210–213, 229
Pfs28 protein, 210, 212–213
Pfs48 protein, 229
Pfs48/45 protein, 208
antigen for transmission-blocking vaccine, 209–213
functions, 209
Pfs230 gene, 209
Pfs230 protein, 208
antigen for transmission-blocking vaccine, 209–213
functions, 209
Plasmodium falciparum, 17–18
clinical manifestations, 42–48
FCB-1 strain, 136
FCR-3 strain, 139–140
FUP strain, 135–136, 143–145
FVO strain, 135–136, 138, 144
genetic crosses, 200, 202
genome, 171, 266, 308, 321
infected red cells, 216–233
Malayan Camp strain, 136, 143
St. Lucia strain, 136
Plasmodium falciparum, 17–18
clinical manifestations, 42–48
Plasmodium gallinaceum, 92, 95–97,
103–105, 202–204, 235–236,
239, 243, 294
Plasmodium knowlesi, 105–106, 109,
116–119, 122–123, 127, 129, 135,
227, 229, 245
Nuri strain, 105
Plasmodium kochi, 39
Plasmodium lophurae, 92, 95–99, 102–
103, 226–227, 313–315
maintained in chickens, 312–313
transport studies, 315
Plasmodium malariae, 18
clinical manifestations, 42–48
Plasmodium ovale, clinical manifestations, 42–48
Plasmodium relictum, 29, 90–91, 93, 95
Plasmodium vivax, 17
clinical manifestations, 42–48
Plasmodium yoelii, 172, 174–175, 271–
272, 280–281
Platt, B. S., 112
Plimmer, H. G., 21
PMMSA, see MSP-1
Pneumococcal pneumonia, 107–108
Polio vaccine, 71, 88–89, 160, 321
Poliovirus, tissue-grown, 160
Pollender, Franz, 6
Porter, James, 132–133
Porter, Rodney, 57, 113, 172
Postfertilization antigens, 210
Potter, Michael, 164
Poxvirus vector, 184, 262
Index

Pregnancy malaria, 221–223, 320
Premunition, 95, 97–98, 292, 301, 318
Primaquine, 45, 275
Prisoners, participation in vaccine trials, 246–251
Professional antigen-presenting cells, 73
Preguanil, 45–46
Proinflammatory response, 66–67
ProtaTek International Inc., 149
Protective antigens, 85
Protective clothing, 36
Proteins, serum, 56
Prout, W. T., 34
Puerperal fever, 5–6
Push programs, 156–157
Pvs25 protein, 210, 229
Pvs28 protein, 210
Pygmalione effect, 157
Pyrethrum spray, 194–196
Pyrimethamine, 46
Qinghaosu, see Artemisinin
QS21, 258
Quartan malaria, 9, 42
Quinine, 12, 14, 16, 38, 44–45, 189, 288
Quinine resistance, 46

$R_0$, 192–193, 215
Rabies, 85–86
Rabies vaccine, 85–88
Rank, R., 97–98
Ray, A., 105
RBP, see Reticulocyte-binding proteins
Recombinant DNA, 164–171
Recombinant proteins, 157, 179–180
Recrudescence, 39, 43
Red blood cell(s), 59
  irradiated parasitized, 305–306
  merozoite invasion of, 181–182, 225–231, 293, 324
  merozoite receptors, 227
MSP-1 binding to, 177
P. falciparum-infected, 216–233

Plasmodium-infected, rosetting, 224–225
Red blood cell membrane, 315–318
Reese, Robert, 140–143, 155, 160–161
Relapse, 39
Relapsing malaria, 39
Research funds, 146–157
Reticulocyte(s), invasion by P. vivax, 231
Reticulocyte-binding proteins (RBP), 169, 231
Reverse transcriptase, 165
Revolutionary War, 47
Rhoptry, 226
Rhoptry antigens, 142
Richard, Eugene, 16
Richards, W. H. G., 143, 236–241, 243
Rieckmann, Karl, 126, 128, 246, 249, 266
Riley, Eleanor, 65–66, 176
Ristic, Miodrag, 148–149, 306–307
RLF vaccine, 257
Robbins, F. C., 160
Rockefeller, John D., 190–191
Rockefeller Foundation Laboratories, 106
Rockefeller Institute for Medical Research, 107–108, 190–191
Rocker culture method, 137–138
Roehl, Wilhelm, 90–91
Roller tube culture, 159
Roman fever, 9
Romanowsky, Dimitri, 43–44
Rosetting, 224–225
Ross, Ronald, 20–26, 37, 188–189, 191–193, 195, 214, 292
rivalry with Grassi, 26–37
Rossan, Richard, 133–134
Rossignol, Hippolyte, 82
Roundworm infection, 303
Roux, Emile, 50, 83, 85–87, 94
RPMI 1640 medium, 138
RTS,S vaccine, 66, 187, 254–261, 267, 273, 299, 311, 320
Rubella vaccine, 88
Russell, Paul F., 235–236, 239
Russell, Phillip, 308, 315
Sadun, Elvio, 143, 229, 302–306
Saint, Robert, 168
Salivary glands, mosquito, 26, 40–42, 235, 242
Salivation, 286
Salmon, Daniel Edward, 108
Salvarsan, 286–287
Sanaria, 265–266, 268
Sanger, Frederick, 166
Sanitation, 188
Saponin, 181–182, 239–240
SBAS2, 277
Scaife, John, 166
Schaeffer, Fritz, 37–38, 286
Schick test, 55
Schistosomiasis, 304–305
Schizont antigens, 167
Schizont vaccine, 128, 143
Schizont-infected cell agglutination (SICA) reaction, 116–117, 121, 217–218
Schmidt, Leon H., 133–134
Schofield, L., 279
“Self,” 59
Semmelweis, Ignaz, 5–6
Sequestration, 216, 317–318
in placenta, 221–223
vaccine to prevent, 216–233
Sergent, Edmond, 94–95, 234
Sergent, Etienne, 94–95, 234
Serum, 50, 59
Serum fractionation, 56
Serum therapy, 55
Sexual harassment, 154
Sherman, Irwin, 96–97, 99, 103, 110, 140, 158, 218, 226, 269–270, 301, 311–318
Shortt, Henry, 39
Shute, P. G., 287
SICA reaction, see Schizont-infected cell agglutination reaction
Siddiqui, Wasim A., 135–138, 144–146, 151–153, 161
Silverman, Paul, 124–129, 264
Sinden, Robert, 204
Singh, J., 105
Sinton, John, 105
Skamene, Emil, 295–296
Slave trade, 9–10
Slim, Sir William, 47
Smallpox, 76
Smallpox eradication, 80
Smallpox vaccine, 71, 77–80, 321, 324–325
Smith, Edgar A., 146–147
Smith, Theobald, 81–82, 108
Sommariva, Giorgio, 286
Soper, Fred L., 194–196
Spanish-American War, 190
“Species barrier,” 322–323
SPf66 vaccine, 184–187
Spieth, Herman, 315
Spirochetes, 286
Spleen, dysfunction in malaria, 42
Spleen cells, 299
Spontaneous generation, 4
Sporozoite(s), 37–38, 40–42
attenuated, 95, 234–251
CSP reaction, 243
formaldehyde-killed, 109
knockout, 281–282
Sporozoite antigens, 271
identification, 251–255
Sporozoite immunoassay, 307
Spray gun, 194
Squalene, 255–256
Squirrel monkeys, 132, 149–151
Staining techniques, 17, 52
blood film, 43–44
Stanley, Harold, 141–142, 160–161
Stauber, Leslie, 133, 270–271
Stem cells, 72
Sterile immunity, 146, 233, 243, 249, 272, 299
Sternberg, George, 13–14, 17
Stevenson, Mary M., 295–298, 311
Stillbirth, 43
Stoll, Norman R., 313
Strain-transcending immunity, 293
Stratman-Thomas, Warren, 288–289
Subunit vaccine, 88, 176, 232, 255–261, 264, 267, 321
Sulfadoxine, 46
Sulfanilamide, 107
Surface antigens, 217
  gamete, 209–213
  ookinete, 210–211
Susceptibility genes, 296–298
Swan-neck flask experiment, 4
Syphilis, tertiary, 38, 105, 246, 285–291
T cells, 67, 70, 74, 98, 271–272, 275, 294, 298–301
  CD8 (killer), 72, 75, 272–273, 275, 283, 299
  cytotoxic, 60, 72–74, 261–262
  in protective immunity, 72–75
  synthesis and release, 72–73
Tafenoquine, 45
Takahashi, Yuzo, 315
Taliaferro, Lucy Graves, 91–95, 132
Taliaferro, William Hay, 91–95, 132, 268–270, 315
Targett, G. A., 110
Tate, P., 38
TBV, see Transmission-blocking vaccine
TBV25H vaccine, 212
T-cell receptors, 73
Tertian malaria, 9, 42
  benign, 43
  malignant, 43
Tetanus, 50, 71
Tetanus vaccine, 321
Thayer, William S., 19
Thomas, Alan W., 129, 181–182
Thrombospondin-related antigenic protein, see TRAP
Thymus, 72
Tight junction, 226, 231
Tiselius, Arne, 56
Tissue culture, 160, 269
Titer, antibody, 53, 110
TNF, see Tumor necrosis factor
Toll-like receptors, 62–63, 67
Tommasi-Crudeli, Corrado, 13
Top, Franklin, 307
Toussaint, Jean-Joseph Henri, 81–83
Toxin, 50–51, 278–280
Toxoid, 55
Transmission of malaria, 188–215, see also Mosquito entries
  mathematical models, 192–193
Transmission-blocking immunity, 206–207
Transmission-blocking vaccine (TBV), 193, 199–215, 322
  antigens for, 207–209
  DNA vaccine, 213
Transport studies, P. lophurae, 315
TRAP (thrombospondin-related antigenic protein), 262–263, 276, 281
Trejdosiewicz, Avril, 174
Treponema, 286
Trigg, Peter, 115–116, 120
Truong, Father Hoang Wuoc, 96–97, 312
Trypan red, 114
Trypanosomes, 93, 107, 114–115, 118, 172
Tryparsamide, 107
Tuberculin, 101
Tuberculosis, 52, 100–101, 116, 291
Tuberculosis vaccine, 87–88
Tumor necrosis factor (TNF), 61–66, 75, 279, 295, 299
Typhoid fever, 265

UIS (up-regulated in infectious sporozoites) genes, 281–282
U.S. Agency for International Development (USAID), 124–129, 140–142

Vaccination, 79
goals, 74–75
Vaccine, see also specific vaccines
antidisease, 278–280
antitoxicity, 278–280
attenuated, see Attenuated strain
blocking merozoite invasion, 225–231
DNA, 88, 155, 157, 213, 220, 261–263, 300, 324
dreams about, 111–130
eye studies, 90–110
economic issues, 325
erthrocytic stage, 99
formalin-killed exoerythrocytic stages, 104
heat-killed, 99
impediments to production, 320–321
liver stage, 268–278, 282–283, 324
monkey, 105–110
mosquito-stage, 199–215
multiantigen, multistage, 263, 322
nasal, 213
to prevent pregnancy malaria, 221–223
to prevent sequestration, 216–233
recombinant protein, 157
rosette-inhibiting, 224–225
schizont, 128, 143

subunit, 88, 176, 232, 255–261, 264, 267, 321
transmission-blocking, see
Transmission-blocking vaccine
whole-parasite, 232
Vaccine-resistant mutants, 322
Vaccinia virus, WR strain, 211
Vaidya, Akhil, 178
van den Berghe, Louis, 242
Vanderberg, Jerome, 241–247
van Leeuwenhoek, Antonie, 2–3, 9
var genes, 218, 292
var3csa gene, 222–223
Variola major, 76–77, 79–80
Variola minor, 76–77
Variola vaccines, 76–77, 79–80
Variolation, 79–80
Varmus, Harold, 179
Venter, Craig, 266
Verhave, J. P., 275
Vessel, Elliot, 314
Vickerman, Keith, 118
Vietnam War, 47, 302
Vincke, Ignace, 242
Viral vaccine, 89
Voller, Alistair, 133, 143

Wagner-Jauregg, Julius, 287
Walliker, David, 166
Walter and Eliza Hall Institute (WEHI), 166–169
Wasielewski, T., 94
Waters, Andy, 129, 182
WEHI, see Walter and Eliza Hall Institute
Weidanz, William P., 97–99, 178, 297–298
Welch, William Henry, 17, 19
Wellcome, Sir Henry, 173
Index

Wellcome Research Laboratories, 172–174, 236–240
Wellde, Bruce, 305
Weller, Thomas, 159–160
White, Nick, 187
White blood cells, 59
Whitmore, Eugene, 91, 94
Whooping cough, 51
Williamson, James, 114–115
Wilson, Allan, 314
Wilson, Iain, 120
Window screens, 36, 190, 198
Woolsorter’s disease, 6–7
Workshop on the Biology and In Vitro Cultivation of Malaria Parasites (WHO, 1977), 139–140
World War I, 47
World War II, 47, 196, 236, 242

Worm vaccine, 125, 241
Wright, J. H., 44


Yellow fever, 194–195
Yellow fever vaccine, 89, 321
Yersin, Alexandre, 50
Yoeli, Meier, 243
Young, Douglas, 116
Young, Martin D., 132–134

Zanzarone, 31
Zavala, Fidel, 272–275, 307
Zeidler, Othmar, 196
Zinsser, Hans, 159
Zolg, Werner, 155