PATHOGENESIS OF HUMAN PULMONARY TUBERCULOSIS
INSIGHTS FROM THE RABBIT MODEL
PATHOGENESIS OF HUMAN PULMONARY TUBERCULOSIS
INSIGHTS FROM THE RABBIT MODEL

ARTHUR M. DANNENBERG, JR., M.D., PH.D.
Center for Tuberculosis Research
Departments of Environmental Health Sciences, Molecular Microbiology and Immunology, and Epidemiology, Bloomberg School of Public Health
Department of Pathology, School of Medicine
Johns Hopkins University, Baltimore, Maryland 21205
Max B. Lurie, M.D. (1893–1966)
Dedication

To Aileen Hart Dannenberg, my treasured wife of 58 years (to date), whose love and continuous support have made my professional career and this book possible.
CONTENTS

Preface xi
Introduction 1
Major contributions of Max B. Lurie and Arthur M. Dannenberg, Jr.

SECTION 1. PATHOGENESIS OF TUBERCULOSIS

1. Overview 7
   Childhood and adult tuberculosis, bacillary virulence, host resistance, contagion, and prevention

2. Stages in the Pathogenesis of Human and Rabbit Tuberculosis 22

3. Types of Human Pulmonary Tuberculosis 34

4. Liquefaction of Caseous Foci and Cavity Formation 65

SECTION 2. IMMUNOLOGY OF TUBERCULOSIS

5. Delayed-Type Hypersensitivity, Cell-Mediated Immunity, and Antibodies in Tuberculosis 97
   Their local and systemic natures; innate immunity

6. Macrophages and Other Cells in Tuberculous Lesions 120
   Including dendritic cells and lymphocytes

SECTION 3. TUBERCULOUS LESIONS

7. Structural Components of Tuberculous Lesions 155

8. Microvascular Density in Tuberculous Lesions 161
   In developing and healing BCG lesions and in tuberculin reactions

Downloaded from www.asmscience.org by
IP:  54.70.40.11
On: Thu, 15 Aug 2019 19:29:01
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Early Pulmonary Lesions in Rabbits</td>
<td>170</td>
</tr>
<tr>
<td>10</td>
<td>Macrophage Turnover, Division, and Activation in Tuberculous Lesions</td>
<td>177</td>
</tr>
<tr>
<td>11</td>
<td>Lurie’s Pulmonary Tubercle-Count Method</td>
<td>196</td>
</tr>
<tr>
<td>12</td>
<td>Natural Airborne Infection</td>
<td>215</td>
</tr>
<tr>
<td>13</td>
<td>Response of Rabbits to Inhaled Tubercle Bacilli Including BCG</td>
<td>230</td>
</tr>
<tr>
<td>14</td>
<td>Characteristics of Resistance and Susceptibility to Tuberculosis in Lurie’s Inbred Rabbits</td>
<td>235</td>
</tr>
<tr>
<td>15</td>
<td>Comparisons of Tuberculosis in Rabbits, Mice, and Guinea Pigs</td>
<td>246</td>
</tr>
<tr>
<td>16</td>
<td>Effects of Cortisone and Adrenocorticotropic Hormone on Tuberculosis</td>
<td>273</td>
</tr>
<tr>
<td>17</td>
<td>Effects of Estrogen, Chorionic Gonadotropin, and Thyroid Hormones on Tuberculosis</td>
<td>285</td>
</tr>
<tr>
<td>18</td>
<td>Effects of Whole-Body X-Irradiation on Tuberculosis</td>
<td>292</td>
</tr>
<tr>
<td>19</td>
<td>Cytokine Production in Primary BCG Lesions</td>
<td>301</td>
</tr>
<tr>
<td>20</td>
<td>Cytokine Production in Reinfection BCG Lesions and in Tuberculin Reactions</td>
<td>312</td>
</tr>
<tr>
<td>21</td>
<td>Vascular Adhesion Molecules in Tuberculous Lesions</td>
<td>327</td>
</tr>
</tbody>
</table>
SECTION 7. TUBERCULOSIS VACCINES

22. Principles and Guidelines for Developing Better Tuberculosis Vaccines 341

23. Characteristics of Rabbit BCG Lesions and Efficacies of BCG and Mycobacterium microti Vaccines 354

SECTION 8. PAST, PRESENT, AND FUTURE

24. Summary and Conclusions 367

25. Suggested Future Research and Unanswered Questions 373

APPENDIXES

A. Award of the Trudeau Medal for 1955 385

B. Obituary of Max B. Lurie, M.D. (1893–1966) 387

C. Publications of Max B. Lurie 389

D. Publications of Arthur M. Dannenberg, Jr. 399

E. Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, 2005 (Table of Contents) 417

F. Collected Abstracts of Chapters in This Volume 419

G. Acknowledgments 429

Glossary 431

Index 439
PREFACE

This book is a review and update of my contributions to the experimental pathology of tuberculosis, as well as those of my mentor Max B. Lurie (see Frontispiece). The book describes 40 years of his scientific contributions, which were followed by 40 years of mine. I was in his laboratory during the first 11 years that I worked in this field.

BACKGROUND

Max B. Lurie, M.D.

Tuberculosis has afflicted many of the past workers in the field or their close family members. Lurie probably caught tuberculosis from his mother, who died from it. He became ill with the disease during his final year at Cornell Medical School, and after graduating in 1921 he went to the National Jewish Hospital for Consumptives in Denver, Colorado, for treatment. While there, he began his career in tuberculosis research (with H. J. Corper as his mentor) and continued working on the host-parasite relationships of this disease for the rest of his life.

When he had recovered from tuberculosis in 1926, he joined the research staff of the University of Pennsylvania’s Henry Phipps Institute for the Cure and Prevention of Tuberculosis, where he spent the rest of his career, attaining the rank of full Professor (in Experimental Pathology). Lurie’s publications are listed in Appendix C.

Most of Lurie’s experiments are summarized in his book *Resistance to Tuberculosis: Experimental Studies in Native and Acquired Defensive Mechanisms* (1). It almost seems that his determination to complete that book kept him alive during the last few years of his life. He died of an acute myocardial infarction in 1966, at the age of 73.

Arthur M. Dannenberg, Jr., M.D.

My mother’s first husband died of tuberculosis 6 months after they were married. As a result, she became a social worker at the Henry Phipps Institute (where Lurie worked). There she met my father, a practicing pediatrician, who devoted each
Tuesday afternoon to the care of tuberculous children in the Institute’s clinic. After clinic, my father would go upstairs to Lurie’s laboratory, where he learned of his latest experiments.

Lurie was an extremely enthusiastic person, and my father came home quite inspired. Therefore, it was only natural that he would introduce me to Lurie when, in 1948, I was deciding whether to pursue a clinical or a research career. I did not realize at that time that Lurie was one of the world’s leading experimental pathologists of tuberculosis.

I was associated with Lurie for about 11 years—first as a postdoctoral fellow from 1948 to 1952, and then as an assistant professor from 1956 to 1964. During this time, I had so many scientific discussions with him that his knowledge of tuberculosis has become an integral part of my own thinking. In fact, I cite Lurie’s principles every time I write or lecture.

Tuberculosis was (and is) one of the major diseases of humankind, especially in developing countries. It kills about 2 million people in the world each year, more than any other infectious disease (2). If I were going to pursue a research career instead of a clinical one, I wanted to contribute to the elimination of a disease important to mankind.

Fortunately, Lurie outlined what I should pursue in tuberculosis research at the beginning of my career, specifically, the role of the macrophage, especially its hydrolytic and metabolic enzymes. Macrophages are the host’s main defense against the bacillus. The role of lymphocytes was just beginning to be recognized at that time. More insight was needed from the disciplines of immunology and biochemistry into how these cell types function. In addition, the histopathology of the disease, as observed under the microscope, needed to be correlated with immunological and biochemical cell functions.

Therefore, I learned the techniques of these (and other) basic sciences and have used them in different stages of my career to understand the role of mononuclear cells in tuberculosis lesions (see my publication list in Appendix D). Concurrently, the whole discipline of histochemistry has evolved. This discipline enables scientists to visualize structural and enzymatic cell characteristics in tissue sections. We in my laboratory, therefore, used histochemistry to gain deeper insight into the pathogenesis of tuberculous lesions and how the host controls them.

THE RABBIT MODEL OF TUBERCULOSIS

Lurie favored the rabbit model of tuberculosis because the disease in this laboratory animal most closely resembles that found in humans (1, 3–5). Caseous necrosis, liquefaction, and cavity formation with bronchial spread of the disease can be readily produced in rabbits. Tuberculous lesions in mice, on the other hand, are granulomas that slowly progress with little or no caseation, and cavities never form. However, mice are an excellent model in which to study cell-mediated immunity in tuberculosis. For such studies, many reagents are commercially available.

Tuberculosis in guinea pigs progresses rapidly with much caseation and hematogenous and lymphatic spread of the disease. It resembles the susceptible form found in infants and immunosuppressed persons, but not the slowly progressing fibrotic cavity form found in immunocompetent humans and rabbits. Guinea pig lesions occasionally cavitate, but significant bronchial spread is rare. Because of these species differences, Lurie began rather early in his career to work with rabbits, after working initially with guinea pigs. I have continued to use the rabbit model.
DERMAL BCG LESIONS
Many of my own studies in the rabbit model were made on developing, peak, and healing dermal BCG lesions. In rabbits, these lesions resemble pulmonary lesions produced by human-type tubercle bacilli in that they develop and then regress. Dermal BCG lesions begin with numerous bacilli injected into one site. Therefore, caseation, liquefaction, and ulceration readily occur. However, for the study of naturally occurring tuberculosis, there is no substitute for aerosol infection, where a single unit of 1 to 3 bacilli in rabbits produces lesions that closely resemble those occurring in human populations.

For each stage of pulmonary lesion development and healing, a rabbit must be sacrificed (euthanized). In contrast, multiple dermal BCG lesions of various ages can be produced in a single rabbit, or multiple lesions started at the same time can be biopsied at various times under local anesthesia. However, the results of such studies must be confirmed in rabbits with no previous biopsy and in rabbits with all lesions of the same age. Nevertheless, the use of multiple lesions on the same rabbit in part compensates for the marked difference in cost of purchase and maintenance between rabbits and mice.

PURPOSE AND USE OF THIS BOOK
The purpose of this book is to present in one place our current understanding of the pathogenesis of tuberculosis derived from Lurie’s and my own research. The book is written for both clinicians and laboratory researchers. Clinicians will read parts of it to gain insight into the pathogenesis of tuberculosis as a guide for the care and treatment of their patients. Laboratory researchers will read parts of it to plan some of their experiments. For such researchers, I have sometimes provided more details and references.

I have used Lurie’s original publications as references for many of the statements made herein and used his book as a reference when it contributed additional information. Statements that I heard personally from him are also referenced to his book.

ORGANIZATION OF THIS BOOK
This book was organized for several types of readers, as follows.

(i) Readers wanting a quick understanding of the pathology and immunology of tuberculosis can read chapter 24, “Summary and Conclusions,” and if more detail is desired, they can read the chapter abstracts, which are assembled as Appendix F.

(ii) Readers wanting information on the individual subjects can read the pertinent chapters. At the head of each chapter, I have provided both an abstract and a list of the main headings within the chapter. These should enable the reader to more rapidly find the information he or she is looking for. The book was written so that each chapter is complete within itself, which results in occasional duplication of text, figures, and references but is a necessity for the reader of only individual chapters.

Finally, (iii) some readers may want to read the entire book for the various orientations presented.

Many chapters contain more experimental details than others. These chapters describe types of tuberculosis research that are usually not performed in other laboratories and are therefore unfamiliar to many readers. Full details on the technology, however, only appear in the original publications cited.

The “see” before a reference number in this book signifies that the reference contains additional information. This information is pertinent but does not necessarily
support the statement to which the reference is attached. Without the “see,” the reference is supportive.

**Note.** Lurie (1) used the words “native” and “acquired” resistance. Today, because of Janeway’s extensive studies (6), the words “innate” and “adaptive” immunity have replaced Lurie’s terminology. In this book, we mostly used Lurie’s terminology, because it seemed more appropriate for tuberculosis in his inbred rabbits.

**OTHER BOOKS ON TUBERCULOSIS**

The classic books on tuberculosis are those of Rich (Johns Hopkins University; 1951) on the immunopathology (7), Canetti (Pasteur Institute; 1955) on the human pathology (8), Lurie (1964) on the experimental pathology (1), and Iseman (2000) on clinical tuberculosis (9). Multiauthored texts by authorities in each respective field are those edited by Bloom (1994) (10), Reichman (2000) (11), Schlossberg (2006) (12), Cole et al. (1995) (13), and Rom and Garay (2004) (14). These multiauthored texts provide more details on the various subjects reviewed herein, but very few studies in the rabbit model of tuberculosis are included.

**REFERENCES**

Antibody
enhancement of local DTH and CMI reactions, 106–107, 108, 110
host resistance to reinfection, role in, 378
role, as elucidated by Lurie’s eye chamber experiments, 107, 109, 111
Antibody-dependent cell-mediated cytotoxicity (ADCC), 432
Antigen-presenting cells (APCs), 99, 113–114, 121–123; see also Dendritic cells
definition, 431
published reviews on presentation, 123
t cell activation, 121–122
Antimicrobials, resistance to, 31, 43, 57–59
Apoptosis, 142–143, 193, 263, 432
Arrested lesions, 28, 37, 38, 60–62
CMI and DTH required for, 101–102
Arthus reaction, 432–433
Atelectasis, 44
Azathioprine, cavity prevention by, 66

B
B cells, 433
BAL (bronchoalveolar lavage), 296
BALT (bronchial-associated lymphoid tissue), 343
Bar Harbor rabbits, 241–242
Basophils, 144
B7.1/B7.2, 433
BCG, see also Mycobacterium bovis
BCG

cytokines in primary lesions, 301–309
cell types containing MCP-1, IL-1β, IL-8, and TNF-α mRNAs, 304
comparison among cytokines, 306–307
cytokine mRNA in cells within tissue sections, 301–304
IFN-γ mRNA identified by RT-PCR, 305
immunohistochemical studies, 305
overview, 301–304
cytokines in reinfection lesions, 312–323
lesion size, ulceration, and healing, 313
local cell infiltration, 313
mononuclear cells and granulocytes in lesions, 315–319
number of tubercle bacilli in, 319
definition, 433
dermal lesions in rabbits
BCG preparations for, 354–355
development and healing, 355–356
healing as measure of host resistance, 359
histopathology, 356–357
number of bacilli in lesions, 357–358
pulmonary lesions compared, 358–359
fate of aerosolized BCG in rabbits, mice, and guinea pigs, 262
intradermal injection to produce caseous necrosis and liquefaction, 68
intravenous in rabbits, Lurie’s experiments with, 359–360
macrophages
activation, 127–128
enzymes released extracellularly, 128–129
heterogeneity in lesions, 129, 131, 133
turnover, activation, and division in healing dermal lesions, 189, 191
in vitro division of activated in BCG lesions, 179
in vitro division of cells containing bacilli in BCG lesions, 179
in vivo [3H]TdR labeling, 179, 180
microvasculature of lesions
histopathology, 163–166
production of developing and healing lesions, 161–162
mononuclear cells
activation in tuberculin reactions and in lesions caused by nonspecific irritants, 192–193
in blood, labeled, 185–186
disappearance from lesions, 182–185
division rate within lesions, 184–185
entry into lesions, 180, 182
rates of activation in primary and reinfection lesions, 187, 189
pulmonary lesions in rabbits, production by intravenous injection, 170–175
rabbit response to inhaled bacilli, 233–234
vaccination
combination vaccines, 349
inapparent lesions and, 61–62
in mice and guinea pigs, 343–344
in monkeys, 258, 260
nonspecific irritants, effect on, 193
recombinant technology improved, 349
strong CMI and weak DTH, 344–345
systemic nature in humans, 360–361
vascular adhesion molecules, 327–336
activation of microvascular endothelium and caseous necrosis, 334–335
in acute inflammatory lesions, 331
in epithelioid cells, 333
functions, 333–334
identification of microvessels in tissue sections of BCG lesions, 329
leukocyte ligands in BCG lesions, 333
overview in, 328–329
in primary BCG lesions, 329–330
quantitation in tissue sections, 329
questions to be answered, 335–336
in reinfection BCG lesions, 331, 332
virulence, 13, 14
X-irradiation effects on dermal BCG lesions, 293

Blood supply
activation of microvascular endothelium and caseous necrosis, 334–335
angiogenesis, regulators of, 167
capillary density, determined by gelatin-colloidal carbon perfusion, 162–163
INDEX

microvascular patency, in mouse pulmonary lesions, 254
microvessels in tissue sections of BCG lesions, 329
pathophysiology of, 167–168
vascular thrombosis role in causing caseous necrosis, 375–376
Bronchial spread
adult-type tuberculosis, 11, 14
cavity formation and liquefaction, 29, 30–31, 42–46
contagiousness, 11–12
Bronchial-associated lymphoid tissue (BALT), 343
Bronchoalveolar lavage (BAL), 296
Burkholderia pseudomallei, 226–227
C
C5a, 24, 433
Calcification of nodules, 37, 38, 45
Capillary density, determined by gelatin-colloidal carbon perfusion, 162–163
Caseous necrosis
activation of microvascular endothelium, 334–335
advanced fibrocaseous tuberculosis, 46–47
caseous tissue as structural component of lesions, 155–156
causes
table of, 156
vascular thrombosis, role of, 375–376
cavity formation, 65–91
healed lesions, 45, 158
liquefaction, 29, 30–31, 42–46, 65–91
progressive lesions, 46
radiography of encapsulated nodules, 38
research, suggested future, 375–376
bacillary growth in liquefied caseum, 379
bacillary survival in solid caseum, 379
stages of tuberculosis and
stage 3, early stage, 25–28
stage 4, progression or arrest of lesion, 28
stage 5, cavity formation, 29, 30–31
Caseous pneumonia, 31, 45, 53, 57
Cathepsin D, 68, 128
Cavity formation, 65–91; see also Liquefaction
aerosolized virulent M. bovis in rabbits, 71–84
background, 71
high-dose experiments, 73, 74–78
histopathology, 79–84
low-dose experiments, 71–72, 74
tuberculin sensitivity, 78–79
analysis of lesions, 59
bronchoscope production in rabbits, 68
delayed-type hypersensitivity (DTH), role of, 66
in guinea pigs, 256, 263
histopathology, rabbit, from aerosolized virulent M. bovis
cavity formation, 78, 79–80
epithelioid cells, 80–81
fibroblasts, 82, 87, 88
granulated macrophages, 80, 82
hemoptysis, 80, 81
lymphocytes and plasma cells, 82–83, 88
metaplastic alveolar epithelium and chemotaxis of alveolar macrophages, 83–84, 88, 89
number of bacilli, 81, 83, 84, 85
hydrolytic enzymes, role of, 66
literature review, 66–71
bronchoscope production of cavities in rabbits, 68
dermal BCG lesions in pilot studies on caseation and liquefaction, 68
distinction between caseation and liquefaction, 67–68
effects of large numbers of bacilli on liquefaction, 68, 71
role of delayed-type hypersensitivity, 66
role of hydrolytic enzymes, 66–67
measuring factors affecting, proposed method for, 90–91
in mice, 263
in monkeys, 263
pathogenesis, 29, 30–31, 42–46, 157–158
in rabbits, 263
recent experiments attempting to reduce, 84–87
Mycobacterium vaccae, studies with, 84, 86
ritonavir, studies with, 86–87
research, suggested future, 375–376
summary, 87, 90–91
tuberculin sensitivity in rabbits and, 78–79
C-C chemokines, 433
CD4, 138, 139, 140, 319, 356
CD8, 99–100, 138, 139, 140, 319, 356
CD (cluster of differentiation), 433
CD1 proteins, 122–123
Cell-mediated immunity (CMI)
acquired cellular resistance (ACR) compared, 102
antibody enhancement of local reactions, 106–107
arrested lesions, required for, 101–102
CMI/DTH ratio
favorable, 100–101
ideal, 374
research, suggested future, 374–375
species variations, 375
control of bacillary growth by, 26–28, 247, 249
definition, 99, 431
in guinea pigs, 263–264
kinetic studies in rabbits, insights on provided by, 193–194
local nature of, 102–104
macrophage turnover, 375
in mice, 259–260, 263–264
Mycobacterium vaccae, effect of, 84
overview, 99, 100
in rabbits, 263–265
similarities to DTH in tuberculosis, 99–100, 263
summary of role in pathogenesis of tuberculosis, 369–370

Downloaded from www.asmscience.org by
IP:  54.70.40.11
On: Thu, 15 Aug 2019 19:29:01
Cell-mediated immunity (CMI) (Continued)
synergism with DTH, 27, 104–105
vaccines producing strong CMI, 344–345
Chemokines, 433; see also Cytokines
Chemotaxins, 24
Chemotaxis, of alveolar macrophages, 83–84
Childhood-type tuberculosis, 8, 9–11, 49–51
Chorionic gonadotropin, effects of, 286
Chronic infections, general characteristics of, 371
CMI, see Cell-mediated immunity (CMI)
Complement system, 112–113
Contagiousness, 11–12
Cord factor, 157
Cortisone
development of disease, effects on, 273–275
withdrawal, effects of, 275–279
CTLs (cytotoxic T lymphocytes), 141–142, 433
C-X-C chemokines, 433
Cynomolgus monkeys, tuberculosis in, 258–259, 263
Cytokines
from CMI-producing lymphocytes, 99
definition, 433
downregulation, causes of, 321, 323
in humans, 307–308
in mice, 308–309
mRNAs, 319, 321
networks, 323
non-antigen-specific nature of, 102
nonspecific and antigen-specific production, 309
in primary BCG lesions, 301–309
cell types containing MCP-1, IL-1, IL-8, and
TNF-α mRNAs, 304
comparison among cytokines, 306–307
cytokine mRNA in cells within tissue sections,
301–304
IFN-γ mRNA identified by RT-PCR, 305
immunohistochemical studies, 305
overview, 301–304
in reinfection BCG lesions, 312–323
lesion size, ulceration, and healing, 313
local cell infiltration, 313
mononuclear cells and granulocytes in lesions,
315–319
number of tubercle bacilli in, 319
in tuberculosis reactions, 312–323
Cytotoxic T lymphocytes (CTLs), 141–142, 433
ideal, 374
research, suggested future, 374–375
species variations, 375
control of bacillary growth by, 26–28, 247
definition, 98, 431
in guinea pigs, 263–264
kinetic studies in rabbits, insights on provided by,
193–194
liquefaction and cavity formation, role in, 66
local nature of, 102–104
macrophage turnover, 375
in mice, 259–260, 263–264
Mycobacterium vaccae, effect of, 84
overview, 98–99
in rabbits, 193–194, 263–265
similarities to CMI in tuberculosis, 99–100, 263
summary of role in pathogenesis of tuberculosis,
368–370
synergism with CMI, 27, 104–105
tissue-damaging, 26–27, 98–99, 155–157, 432
tuberculin sensitivity, 98
tuberculin skin reaction and, 105–106
vaccines producing weak DTH, 344–345
Dendritic cells
as adjuvants, 122
as antigen-presenting cells (APCs), 99, 121–123
CD1 proteins, 122–123
conventional, 122
major histocompatibility complex (MHC),
122–123
organ effects on, 122
pattern recognition receptors (PRR), 98
plasmacytoid, 122
published reviews on antigen presentation, 123
T-cell activation, 121–122
tolerogenic, 122
as vaccine carriers, 347
Dermal lesions, in rabbits
BCG preparations for, 354–355
development and healing, 355–356
healing as measure of host resistance, 359
histopathology, 356–357
number of bacilli in lesions, 357–358
pulmonary lesions compared, 358–359
Dexamethasone, reactivation of healing pulmonary
tubercles by, 279–280
DHEA (dehydroepiandrosterone), 282
Diapedesis, 328
DNA vaccines, 349
Dormancy, 104–105, 124, 126, 263–264
Drugs, suggested future research
acting on bacillus, 380–381
acting on host, 380
DTH, see Delayed-type hypersensitivity (DTH)

E
ELAM (endothelial-leukocyte adhesion molecule),
327–333, 433; see also Vascular adhesion
molecules
Emphysematous bleb or bulla, 45
Empyema, 49
Encapsulated nodules, 38, 40
Eosinophils, 144
Epithelioid cells, 133; see also Langhans’ giant cells
adhesion molecules in, 333
definition, 433
histopathology in aerosolized virulent M. bovis in
rabbits, 80–81
immature, 28, 103, 133
mature, 26, 38, 49, 80–81, 103, 133
in miliary tubercles, 42
ESAT-6 antigen, 106
Establishment of infection, 35–38
airborne infections, natural
resistance to establishment of lesions by bovine-
type bacilli, 216–218
resistance to establishment of lesions by human-
type bacilli, 223–224
factors influencing, 15–16
subapical localization, 54–55
vaccine, effects of
macroscopic tubercle, 342–343
microscopic tubercle, 342
Estrogen, effects of, 285–286
Exudative lesions, 39, 41, 42

F
Fas, 433
Fas ligand, 433
Fatty acids, toxic, 31
Feldman, William H., 385–386
Fibrin meshworks, 256
Fibroblasts, 144
Fibrocaseous tuberculosis, advanced, 46–47, 54
Fibrosis, 45
Filters, HEPA, 16, 17, 18, 19
N-Formyl-methionyl-leucyl-phenylalanine, 24
Freezing and thawing, effect on infectivity, 203–204

G
β-Galactosidase, 67, 102–104, 127
GALT (gut-associated lymphoid tissue), 343
Gamma interferon (IFN-γ), 99, 106, 124, 141, 305–308, 433
Gelatin-colloidal carbon perfusion, 162–163
Genetic resistance, 37–38
in mice, 251, 253
tubercle-count method, determination by, 204, 207
Ghon complex, 11, 37, 49–52, 58
Glossary, 431–436
Glucocorticoids
ACTH effects, 280–282
development of disease, effects of cortisone on,
273–275
reactivation of healing pulmonary tubercles by,
279–280
withdrawal, effects of, 275–279
Granulation tissue, 44, 59, 155
Granulocytes, 143–144, 376
in primary and reinfection BCG lesions, 315–319
Granuloma, macrophage turnover in mouse, 193
Growth curves, bacillary
guinea pig, 254–255
mouse, 247
Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, CDC,
Appendix E, 417–418
Guinea pigs
bacillary titers in stationary stage after aerosol
infection, 261–262
establishment and progress of tuberculosis, 224
immunization of, 256, 343–344
inbred strains, 256
organ resistance, 262
pulmonary tubercle counts in, 207, 210
tuberculin sensitivity, 262
tuberculosis in, 254–257
bacillary growth curves, 254–255
cavity formation, 256, 263
cell-mediated immunity (CMI), 263–264
characteristics of lesions, 260
comparison to mice, humans, and rabbits,
259–260
delayed-type hypersensitivity (DTH), 263–264
fate of aerosolized BCG, 262
fibrin meshworks, 256
gross pathology, 255–256
histopathology, 256
immunization, 256
Koch phenomenon, 257
virulence of inhaled bacilli, 260–261
Gut-associated lymphoid tissue (GALT), 343

H
Head cover, 17, 18, 19
Healing
caseous necrosis, 45, 158
cytokines in reinfection BCG lesions, 313
dermal BCG lesions in rabbits, 355–356
macrophage turnover, activation, and division in
BCG lesions, 189, 191
as measure of host resistance, 241, 359
reactivation of healing pulmonary tubercles by
glucocorticoids, 279–280
Heat shock protein 65, 433
Hematogenous spread
in childhood-type tuberculosis, 8, 9–11
miliary tuberculosis, 40–42
Hemoptysis
cavity formation and, 44
histopathology, 80, 81
HEPA filters, 16, 17, 18, 19
Histopathology
aerosolized virulent M. bovis lesions in rabbits,
79–84
dermal BCG lesions in rabbits, 356–357
Histopathology (Continued)
guinea pig, tuberculosis in, 256
hemospyosis, 80, 81
microvascular-cell interactions, 163–167
BCG lesions, 163–166
tuberculin reactions, 164, 167
mouse pulmonary tuberculosis lesions, 253–254
HIV/AIDS, 59–60, 433
Hoods, 17, 18, 19
Hormones
ACTH effects, 280–282
androstenediol (AED), 282
chorionic gonadotropin, effects of, 286
dehydroepiandrosterone (DHEA), 282
estrogen, effects of, 285–286
glucocorticoids
ACTH effects, 280–282
development of disease, effects of cortisone on,
273–275
reactivation of healing pulmonary tubercles by,
279–280
withdrawal, effects of, 275–279
thyroid hormones, effects of, 286–291
Host-parasite interactions
host response, suggested research on local control
of, 373
principles of, 370–372
summary of, 367
Human disease, types of, 9–11
adult-type tuberculosis, 11, 12, 13, 14, 15
childhood-type tuberculosis, 8, 9–11
Hydrolytic enzymes, 31
in activated macrophages, 128
liquefaction and cavity formation, role in, 66
Immunocompromised hosts, 59–60, 123
Immunoglobulin G (IgG), 433
Immunohistochemical studies for cytokine proteins,
305
Immunology of tuberculosis, 95–145
acquired cellular resistance (ACR)
definition, 431
duration and specificity, 102
overview, 102
recall upon reinfection, 111–112
adaptive immunity
definition, 431
innate immunity relation to, 112–114
nonspecific and antigen-specific immune
responses in, 114
antibody enhancement of local DTH and CMI
reactions, 106–107, 108, 110
antibody role, as elucidated by Lurie’s eye chamber
experiments, 107, 109, 111
antigen-presenting cells (APCs), 99, 113–114,
121–123
arrested lesions, CMI and DTH required for,
101–102
cell-mediated immunity (CMI)
acquired cellular resistance (ACR) compared, 102
antibody enhancement of local reactions, 106–107
arrested lesions, required for, 101–102
control of bacillary growth by, 26–28, 247, 249
definition, 99, 431
in guinea pigs, 263–264
kinetic studies in rabbits, insights on provided by,
193–194
local nature of, 102–104
macrophage turnover, 375
in mice, 259–260, 263–264
Myobacterium vaccae, effect of, 84
overview, 99, 100
in rabbits, 263–265
similarities to DTH in tuberculosis, 99–100, 263
summary of role in pathogenesis of tuberculosis,
369–370
synergism with DTH, 27, 104–105
vaccines producing strong CMI, 344–345
cells involved, 120–145
antigen-presenting cells, 99, 113–114, 121–123
epithelioid cells, 133
granulocytes, 143–144
Langhans’ giant cells, 133, 136
lymphocytes, 137–140
macrophages, 104, 123–133
mononuclear cell turnover, 136–137
NK cells, 140–141, 142
table of, 121
CMI/DTH ratios, 100–101
favorable, 100–101
ideal, 374
research, suggested future, 374–375
species variations, 375
delayed-type hypersensitivity, 98–99
DTH and CMI similarities, 99–100
DTH and CMI synergism, 27, 104–105
innate immunity
definition, 431
overview, 98
relation to acquired (adaptive) immunity, 112–114
macrophage activation, 104
systemic immunity, 104
tuberculin skin test
booster phenomenon in repeated testing, 105–106
size of reaction, prognostic value of, 105
Immunosuppression, effects of, 59–60
Immunotherapy
dendritic cells, 347
Mycobacterium vaccae, 17, 77, 347
research, suggested future, 380
Inapparent lesions
in humans, 60–62
in rabbits, 62
Inducible nitric oxide synthase (iNOS), 433
Infectedi, freezing and thawing effect on, 203–204
Inhalation of bacilli
bacillary titers in stationary stage after aerosol infection, 261–262
fate of BCG in rabbits, mice, and guinea pigs, 262
Lurie’s tubercle-count, 206, 208–209
number inhaled, 15–16
rabbit response to, 233–234
virulence of bacilli in rabbits, mice, and guinea pigs, 260–261
X-irradiation effects on virulent human-type bacilli, 296–297
Innate immunity
definition, 431
overview, 98
relation to acquired (adaptive) immunity, 112–114
iNOS (inducible nitric oxide synthase), 433
Intercellular adhesion molecule (ICAM), 327–333, 433–434; see also Vascular adhesion molecules
Interleukins
definition, 434
IL-2, 307, 434
IL-10, 113, 307, 434
IL-12, 113–114, 141, 307, 434
Th cell production of, 138
Intracellular dormancy, 263–264
Isocitrate lyase, 124
K
Knockout mice, 434
Koch phenomenon, 257, 434
Koch, Robert, 26

L
Labeling of mononuclear cells
in vivo [3H]TdR labeling, 179, 180
Langhans’ giant cells, 38, 39, 40, 42, 133, 136
Laryngitis, tuberculous, 56, 71
Latency, 126; see also Dormancy
Leukocyte ligands in BCG lesions, 333
Leukocytes, diapedesis of, 328
Leukotriene B4, 4
Liquefaction, 65–91
aerosolized virulent M. bovis in rabbits, 71–84
background, 71
high-dose experiments, 73, 74–78
histopathology, 79–84
low-dose experiments, 71–72, 74
tuberculin sensitivity, 78–79
bronchogenic spread and, 42–46
caseation compared, 67–68
causes and results, 67, 157–158
histopathology, rabbit, with aerosolized virulent M. bovis
cavity formation, 78, 79–80
epithelioid cells, 80–81
fibroblasts, 82, 87, 88
granulated macrophages, 80, 82
hemoptysis, 80, 81
lymphocytes and plasma cells, 82–83, 88
metaplastic alveolar epithelium and chemotaxis of alveolar macrophages, 83–84, 88, 89
number of bacilli, 81, 83, 84, 85
literature review, 66–71
bronchoscope production of cavities in rabbits, 68
dermal BCG lesions in pilot studies on caseation and liquefaction, 68
distinction between caseation and liquefaction, 67–68
effects of large numbers of bacilli on liquefaction, 68, 71
role of delayed-type hypersensitivity, 66
role of hydrolytic enzymes, 66–67
measuring factors affecting, proposed method for, 90–91
in pathogenesis process, 29, 30–31
recent experiments attempting to reduce, 84–87
Mycobacterium vaccae, studies with, 84, 86
ritonavir, studies with, 86–87
research, suggested future, 376–377
summary, 87, 90–91
Logarithmic growth
end of by DTH and CMI, 25–28, 247, 249
within macrophages, 24–25
Long, Esmond R., 387–388
Lurie, Max B.
antibody role, as elucidated by eye chamber experiments, 107, 109, 111
Lurie, Max B. (Continued)
award of Trudeau medal for 1955, Appendix A, 385–386
contributions of, 1–2
invasive BCG experiments, 359–360
natural airborne infection experiments, 215–224
obituary, Appendix B, 387–388
publications, Appendix C, 389–398
pulmonary tuberculosis-count method, 196–210
Lurie’s inbred rabbits
adrenocorticotropic hormone (ACTH), 280–282
airborne infections, natural, 215–224
resistance to establishment of lesions by bovine-type bacilli, 216–218
resistance to establishment of lesions by human-type bacilli, 223–224
resistance to progress of pulmonary tuberculosis by bovine-type bacilli, 218–223
resistance to progress of pulmonary tuberculosis by human-type bacilli, 224
characteristics of lesions in, 260
fate of, 241
histopathology of aerosolized virulent M. bovis in rabbits, 80, 82
heterogeneity
in BCG lesions, 129, 131, 133
in pulmonary lesion in rabbits, early activation and division of blood-borne, 170–175
in vitro division of activated in pulmonary alveolar
activation, 54–55
chemotaxis, 83–84
definition, 432
division of activated in early lesions in rabbits, 175
ingestion of tubercle bacilli, 16, 22–23, 36
innate immunity and, 98, 114
location in lesion, 37
logarithmic growth of bacilli within nonactivated, 24–25
microbicidal power of, 16
role in establishment of grossly visible primary tubercles, 200
susceptibility versus resistance, 37–38
vaccine effects, 342
X-irradiation, effects of, 293–296
bacillary survival within, 379
blood-borne, 24–25, 36–37, 170–175
in caseous tissues, 155–156
chemotaxins, 24
definition, 432
delayed-type hypersensitivity (DTH) killing of, 26–28
division
of alveolar activated in early lesions in rabbits, 175
in early pulmonary lesions in rabbits, 155–156
in healing dermal BCG lesions, 189, 191
in vitro division of activated in BCG lesions, 179
in vitro division of cells containing bacilli in BCG lesions, 180
enzymes released extracellularly in BCG lesions, 128–129
fate of mycobacteria within, 123–124
granulated
histopathology of aerosolized virulent M. bovis in rabbits, 80, 82
Macaca fascicularis, 258–259
Macaca mulatta, 257–258
Macrophage inflammatory proteins (MIPs), 434
Macrophages, 123–133; see also Epithelioid cells
activation, 54–55, 99, 100, 104, 126–128
in healing dermal BCG lesions, 189, 191
in vitro division of activated in BCG lesions, 179
adrenocorticotropic hormone (ACTH), 280–282
airborne infections, natural, 215–224
resistance to establishment of lesions by bovine-type bacilli, 216–218
resistance to establishment of lesions by human-type bacilli, 223–224
resistance to progress of pulmonary tuberculosis by bovine-type bacilli, 218–223
resistance to progress of pulmonary tuberculosis by human-type bacilli, 224
characteristics of lesions in, 260
fate of, 241
histopathology of aerosolized virulent M. bovis in rabbits, 80, 82
heterogeneity
in BCG lesions, 129, 131, 133
causes, 131, 133
in vitro division
of activated in BCG lesions, 179
of cells containing bacilli in BCG lesions, 179
labeling of
in vitro [3H]Tdr labeling, 178–179
in vivo [3H]Tdr labeling, 180
location in lesion, 37, 59
nonspecific activation, 22–23, 54
in pulmonary lesion in rabbits, early activation and division of blood-borne, 170–175
in vitro division of activated pulmonary alveolar, 175

M
Mac-1, 333
receptors, 123
turnover, 136–137
in healing dermal BCG lesions, 189, 191
in mouse tuberculous granulomas, 193
research, suggested future, 375
Major histocompatibility complex (MHC)
activation of microvascular endothelium contribu-
tion to caseous necrosis, 334–335
cytotoxic T cells and, 142
dendritic cells, 122–123
NK cells, 140
Masks, 16, 19
Mast cells, 144
MCP-1 (monocyte chemoattractant [activating] pro-
Medical radiation, public health consequences of,
297–298
Meliodosis, 226–227
Meningitis, tuberculous, 58
Metaplastic alveolar epithelium
histopathology of aerosolized virulent
M. bovis in rabbits, 83–84, 88, 89
Metaplastic bronchial epithelium, 45
MHC, see Major histocompatibility complex (MHC)
Mice
cytokines, 308–309
establishment and progress of tuberculosis, 224
immunization of, 343–344
meliodiosis, immunization and resistance to,
226–227
pulmonary lesions
histopathology, 253–254
microvascular patency, 254
pulmonary tubercle counts in, 207, 210
tuberculin sensitivity, 262
tuberculosis in, 247–254
apoptosis, 263
bacillary growth curves and type of disease,
247
bacillary titers in stationary stage after aerosol
infection, 261–262
bovine-type bacilli, 251
cavity formation, 263
cell-mediated immunity (CMI), 263–264
characteristics of lesions, 260
comparison to rabbits, humans, and guinea pigs,
259–260
delayed-type hypersensitivity (DTH), 263–264
fate of aerosolized BCG, 262
genetic differences in resistance, 251, 253
human-type bacilli, 251
logarithmic stage of growth, ending, 247, 249
stationary stage of growth, maintaining, 249
tissue necrosis, 249–251, 263
virulence of inhaled bacilli, 260–261
Microvascular power, of pulmonary alveolar
macrophages, 16
Microvascular density in tuberculous lesions, 161–168
angiogenesis, regulators of, 167
blood supply, pathophysiology of, 167–168
capillary density, determination of, 162–163
histopathology of microvascular-cell interactions,
163–167
BCG lesions, 163–166
tuberculin reactions, 164, 167
overview, 161
production of BCG lesions and tuberculin reac-
tions, 161–162
Microvascular endothelium, activation and caseous
necrosis, 334–335
Microvascular patency, in mouse pulmonary lesions,
254
Microvessels, identification in tissue sections of BCG
lesions, 329
Miliary tuberculosis, 40–42, 43, 44, 61
MIPs (macrophage inflammatory proteins), 434
Monkeys, tuberculosis in, 257–259, 263
Monocyte chemoattractant protein 1, 24
Monocyte chemoattractant (activating) protein 1
Monocytes, symbiotic growth of bacilli within non-
activated, 24–25
Mononuclear cells, see also Macrophages
BCG lesions
activation in tuberculin reactions and in lesions
caused by nonspecific irritants, 192–193
in blood, labeled, 185–186
disappearance from lesions, 182–184
division rate within lesions, 185
entry into lesions, 180, 182
rates of activation in primary and reinfection
lesions, 187, 189
definition, 434
labeling
in vivo [3H]TdR labeling, 180
in primary and reinfection BCG lesions, 315–319
turnover, 136–137
Mycobacterium bovis, aerosolized virulent in rabbits,
79–84
histopathology
cavity formation, 78, 79–80
epithelioid cells, 80–81
fibroblasts, 82, 87, 88
hemoptysis, 80, 81
lymphocytes and plasma cells, 82–83, 88
metaplastic alveolar epithelium and chemotaxis
of alveolar macrophages, 83–84, 88, 89
number of bacilli, 81, 83, 84, 85
Mycobacterium bovis BCG
intradermal injection to produce caseous necrosis
and liquefaction, 68
macrophage activation, 127–128
macrophage enzymes released extracellularly,
128–129
macrophage heterogeneity in lesions, 129, 131,
133
virulence, 13, 14
**Mycobacterium microti**

vaccine efficacy in New Zealand White rabbits, 363

virulence, 14

**Mycobacterium tuberculosis**

*Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings*, CDC, Appendix E, 417–418

mutants as possible new vaccines, 349

strain virulence, 13–15

virulence by Lurie tubercle-count method

CDC1551 (Oshkosh) strain, 201, 203, 204

Erdman strain, 203

H37Rv strain, 201, 202, 203, 204

**Mycobacterium vaccae**

effect on cavity formation, 84, 86

immunotherapy, 17, 347

for active tuberculosis from inhalation of virulent bovine-type bacilli, 77

**N**

Necropsies, safety precautions for, 18

Necrosis, see Caseous necrosis

Neutrophil attractant-activating protein 1 (NAP-1), 434

Nitric oxide synthase (NOS), 123, 124

NK (natural killer) cells, 140–141, 142, 434

**O**

Old tuberculin, 434

Opsonins, 434

Organ resistance, 102–104, 158–159

guinea pigs, 262

rabbits, 262

research, suggested future, 373–374

Ossification, 38, 45

**P**

Parasite-host interactions

host response, suggested research on local control of, 373

principles of, 370–372

summary of, 367

Pathogenesis

liquefaction of caseous foci and cavity formation, 65–91

aerosolized virulent *M. bovis* in rabbits, 71–84

bronchoscope production of cavities in rabbits, 68

dermal BCG lesions in pilot studies on caseation and liquefaction, 68

distinction between caseation and liquefaction, 67–68

effects of large numbers of bacilli on liquefaction, 68, 71

literature review, 66–71

measuring factors affecting, proposed method for, 90–91

recent experiments attempting to reduce, 84–87

type of delayed-type hypersensitivity, 66

role of hydrolytic enzymes, 66–67

summary, 87, 90–91

**overview**, 7–19

contagiousness, 11–12

establishment of pulmonary lesion, factors influencing, 15–16

prevention of clinical disease, 17–19

resistance, factors influencing, 16–17

size of infectious particles, 12–13

types of human disease, 9–11

virulence of bacillary strains, 13–15

stages, 22–31

stage 1, ingestion of bacilli by macrophages, 22–23

stage 2, logarithmic growth of bacilli within macrophages, 24–25

stage 3, end of logarithmic growth by DTH and CMI, 25–28

stage 4, progression or arrest of caseous lesions, 28

stage 5, cavity formation and bronchial spread of disease, 29, 30–31

summary, 367–368

table of, 30

types of human pulmonary tuberculosis, 9–11, 34–62

adult-type tuberculosis, 11, 12, 13, 14, 15, 51–52

advanced fibrocaseous, 46–47

cavitary lesions, analyses of, 59

childhood-type tuberculosis, 8, 9–11, 49–51

eyear primary lesion, 38

encapsulated caseous or calcified nodules, 38

establishment of infection, 35–38

exudative lesions, 39, 41, 42

in immunocompromised host, 59–60

inapparent lesions, 60–62

liquefied caseous lesions, 42–46

miliary, 39–42

multidrug-resistant bacilli, 57–59

pneumonia and pleurisy, 47–49

progressive, locally destructive lesions, 46

proliferative lesions, 38–39, 40, 42

subapical localization, 51–57

**table**, 35

Pathogenicity, virulence of bacillary strain and, 13–15, 24

Pattern recognition receptors (PRR), 98, 113–114

PBMC, see Peripheral blood mononuclear cells

Pepstatin, 67

Perforin, 142

Pericarditis, 48

Peripheral blood mononuclear cells (PBMC), 307–308

Persistence, of tubercle bacilli, 158

Phagosomes, 123–124

Phosphate-specific transport protein 1 (PstS-1), 435

Plasma cells

definition, 435
histopathology of aerosolized virulent *M. bovis* in rabbits, 82–83, 88
Plasmacytoid dendritic cells, 122
Plethysmograph, 435
Pleurisy, 48–49

**Pneumonia**
- caseous pneumonia, 31, 45, 53, 57
- multidrug-resistant, 59
- overview, 47–49
- rupture of liquefied lesion and, 44
- Polymorphonuclear cells (PMNs), 143–144
- interleukin mRNAs in, 321
- in primary and reinfection BCG lesions, 315–319
- **PPD (purified protein derivative), 435; see also Tuberculin skin test**

**Prevention of clinical disease, 17–19**

**Primary lesion, early, 38**

**Prognostic tests, 377–378**

**Programmed cell death, see Apoptosis**

**Progression, prognostic tests for, 377–378**

**Progressive lesions, 46**

**Proliferative lesions, 38–39, 40, 42**

**PRR, see Pattern recognition receptors (PRR)**

**PstS-1 (phosphate-specific transport protein 1), 435**

**Public health consequences of medical radiation, 297–298**

**Pulmonary alveolar macrophage, see Alveolar macrophages**

**Pulmonary lesion**
- caseous necrosis
  - cavity formation, 29, 30–31
  - early stage, 25–28
  - progression or arrest of lesion, 28
  - dermal BCG lesions compared in rabbits, 358–359
  - factors influencing establishment of, 15–16
  - establishment of infection, 16
  - microbicidal power of pulmonary alveolar macrophages, 16
  - number of bacilli inhaled, 15–16
- mouse
  - histopathology of, 253–254
  - microvascular patency of, 254
  - in rabbits, early, 170–175
  - macrophages, activation and division of blood-borne, 170–175
  - macrophages, division of activated pulmonary alveolar, 175
  - production by intravenous injection of bacilli, advantages of, 170
  - reactivation of healing pulmonary tubercles by glucocorticoids, 279–280
  - resistance to progress in Lurie’s rabbits
    - bovine-type bacilli, 218–223
    - human-type bacilli, 224
- Pulmonary lesion-count method, Lurie’s, 196–210
- Purified protein derivative (PPD), 435; see also Tuberculin skin test

**R**

**Rabbits**
- airborne infections, natural, 215–227
- Lurie’s experiments, 215–224
- Riley’s experiments, 224–226
- Bar Harbor inbred, 241–242
- BCG, intravenous, 359–360
- BCG dermal lesions
  - BCG preparations for, 354–355
  - development and healing, 355–356
  - healing as measure of host resistance, 359
  - histopathology, 356–357
  - number of bacilli in lesions, 357–358
  - pulmonary lesions compared, 358–359
  - commercial inbred, 242
  - comparison of tuberculosis in humans, 226
- histopathology of lesions from aerosolized virulent *M. bovis*, 79–84
- Lurie’s inbred
  - adrenocorticotropic hormone (ACTH), 280–282
  - airborne infections, natural, 215–224
  - characteristics of lesions in, 260
  - fate of, 241
  - genetic experiments, 238–241
  - healing rate of dermal lesions as method of determining resistance, 241
  - history and description of, 235–236
  - intradermal BCG vaccine in, 361–363
  - relative resistance of strains, 236
  - resistance and susceptibility to tuberculosis, 237–238
- Lurie’s tubercle-count method, 196–210
- model of tuberculosis, advantages of, 199–200
- organ resistance, 262
- pulmonary lesion, early, 170–175
- macrophages, activation and division of blood-borne, 170–175
- macrophages, division of activated pulmonary alveolar, 175
- production by intravenous injection of bacilli, advantages of, 170
- response to inhaled bacilli
  - BCG, 233–234
  - bovine-type bacilli, 231–233
  - human-type bacilli, 233
  - Lurie’s resistant rabbits, 231–233
  - Lurie’s susceptible rabbits, 231
- New Zealand White rabbits, 233
- strains, new resistant and susceptible, 378
- Thorbecke, 242–244
- tuberculin reactions, 358
- tuberculin sensitivity, 262
- tuberculosis in, 247, 248
- bacillary titers in stationary stage after aerosol infection, 261–262
- cavity formation, 263
- cell-mediated immunity (CMI), 263–265
- characteristics of lesions, 260
Rabbits (Continued)
comparison to mice, humans, and guinea pigs, 259–260
delayed-type hypersensitivity (DTH), 263–265
fate of aerosolized BCG, 262
virulence of inhaled bacilli, 260–261
X-irradiation effects, 297
vaccine
efficacy of BCG in New Zealand White rabbits, 363
efficacy of M. microti in New Zealand White rabbits, 363
maximal effectiveness, 348–349
van Zutphen, 241
Radiation (X-irradiation), 292–298
alveolar macrophage from granulomatous lungs, effects on, 294–296
dermal BCG lesions, effects on, 293
inhalation of virulent human-type bacilli, effects on, 296–297
lethal dose, 293
public health consequences of medical radiation, 297–298
pulmonary alveolar macrophage populations, effects on, 293–294
in rabbits, 297
recovery from effects of, 296
Radiographs
of encapsulated nodules, 38
lesion size, 38
Reactivation, 52, 59, 279–280
Reactive oxygen intermediates (ROIs), 435
Recombinant technology improved vaccines, 349
Regression, prognostic tests for, 377–378
Regulatory (suppressor) T lymphocytes, 138, 435
Reinfection, 51–52
acquired cellular resistance (ACR) recall, 111–112
antibody role in resistance to, 378
cytokines in BCG lesions, 312–323
lesion size, ulceration, and healing, 313
local cell infiltration, 313
mononuclear cells and granulocytes in lesions, 315–319
number of tubercle bacilli in, 319
rates of activation of mononuclear cells in BCG lesions, 187, 189
vascular adhesion molecules in BCG lesions, 331, 332
Research, suggested future, 373–384
on the bacillus
growth in liquefied caseum, 379
survival in air, 378–379
survival in solid caseum, 379
survival within macrophages, 379
virulence, 379–380
on drugs
acting on bacillus, 380–381
on the host
antibody role in host resistance to reinfection, 378
CMI/DTH ratio, 374–375
DTH and CMI and macrophage turnover, 375
granulocytes, role of, 376
host response, local control of, 373
lesions produced by live and dead tubercle bacilli, comparisons of, 378
liquefaction and cavity formation and prevention, 375–376
organ resistance and its implications, 373–374
prognostic tests that reflect disease progression and regression, 377–378
rabbit strains, new resistant and susceptible, 378
vascular thrombosis, role in caseous necrosis and inhibition of bacillary growth, 375–376
on immunotherapy, 380
on vaccines, 380
Resistance
acquired cellular resistance (ACR), 102, 111–112
in adults versus children, 51
airborne infections, natural
to establishment of lesions by bovine-type bacilli, 216–218
to establishment of lesions by human-type bacilli, 223–224
to progress of pulmonary tuberculosis by bovine-type bacilli, 218–223
to progress of pulmonary tuberculosis by human-type bacilli, 224
antibody role in, 378
bovine-type and human-type bacilli, 159
factors influencing, 16–17
geneic, 37–38, 204, 207, 251, 253
healing as measure of host resistance, 241, 359
host
healing as measure of, 241, 359
tubercle-count to determine, 204
to melioidosis, 226–227
mouse strains, 251, 253
new rabbit strains, 378
organ, 102–104, 158–159, 263, 373–374
species, 158–159
versus susceptibility, 24–25, 37–38
symbiotic growth of bacilli within macrophages, 24–25, 37–38
of tubercle bacilli to antimicrobials, 31, 57–59
Respirators, 16, 17
Reverse transcription-polymerase chain reaction, see RT-PCR
Rhesus monkeys, tuberculosis in, 257–258, 259, 263
Riley, R. L., 224–226
Ritonavir, studies with, 86–87
RNase, 68, 128
ROIs (reactive oxygen intermediates), 435
Room air sampling, 226
RT-PCR (reverse transcription-polymerase chain reaction)
definition, 435
IFN-γ mRNA identified by, 305

S
Satellite lesions, 46
Shwartzman phenomenon, 435
Simon foci, 53
Size, of infectious particles, 12–13
Stages in pathogenesis, 22–31
stage 1, ingestion of bacilli by macrophages, 22–23
stage 2, logarithmic growth of bacilli within macrophages, 24–25
stage 3, end of logarithmic growth by DTH and CMI, 25–28
stage 4, progression or arrest of caseous lesions, 28
stage 5, cavity formation and bronchial spread of disease, 29, 30–31
table of, 30
STAT-1, 124
Strain, virulence of, 13–15
Subapical localization
in adult-type tuberculosis, 51–52
causes of, 52–54
physiology of apical versus basal pulmonary regions, 53–54
source of bacilli, 52–53
establishment of lesions, effect on, 54–55
progress of lesions, effect on, 55–57
Summary
host-parasite interactions, 367
pathogenesis, role of DTH and CMI in, 368–370
pathogenesis, stages, 367–368
Suppressor T-cells, 138
Surfactant proteins, 113
Symbiotic growth of bacilli within nonactivated macrophages, 24–25
Systemic immunity, 104

T
T cell
activation by dendritic cells, 121–122
cytotoxic, 141–142, 433
gamma-delta (γδ), 138–140
helper, 138, 435–436
memory, 140
regulatory, 138, 435
TGF-β (transforming growth factor beta), 436
Th cells, 138, 435–436
Thorbecke rabbits, 242–244
Thyroid hormones, effects of, 286–291
Thyroidectomy, 289–291
Thyroxine, effects of, 286–291
Tissue damage
causes, 156–157
delayed-type hypersensitivity (DTH), 26–27, 98–99, 155–157
Tissue necrosis in mice, 249–251, 263
Titors, in stationary stage in rabbits, mice, and guinea pigs, 261–262
TNF-α (tumor necrosis factor alpha), 99, 141, 304–308, 320–321, 323, 436
Tolerogenic dendritic cells, 122
Toll-like receptors, 112, 113, 123
Transforming growth factor beta (TGF-β), 436
Triiodothyronine, effects of, 286–291
Trudeau medal for 1955, 385–386
Tubercle bacilli
dormancy, 124, 126, 263–264
ending of logarithmic growth by DTH and CMI, 25–28
ingestion by macrophages, 16, 22–23, 36, 123–124
inhaled, number, 15–16
inhibition of growth, 375–376
intracellular versus extracellular growth, 43
logarithmic growth within macrophages, 24–25
number in dermal rabbit BCG lesions, 357–358
peristence, 158
research, suggested future
growth in liquefied caseum, 379
survival in air, 378–379
survival in solid caseum, 379
survival within macrophages, 379
virulence, 379
resistance, 31, 43
virulence
research, suggested future, 378–380
strain, 13–15, 24
Tubercle-count method, Lurie’s, 196–210
advantages of rabbit model of tuberculosis, 199–200
aerosol infections versus intravenous infections, comparison of, 206–207, 210
bacillary virulence, 207
host genetic resistance, 207
vaccine efficacy, 207
alveolar macrophage role in establishment of grossly visible primary tubercles, 200
comparison of counts, 204–206
clinical Mycobacterium tuberculosis isolate, 201, 203, 204
freezing and thawing, effect on infectivity, 203–204
human-type bacilli (H37Rv), 201, 202, 203, 204
overview, 197–198
variability of counts, 205, 206
virulence, determination of
bovine-type bacilli, 201
clinical Mycobacterium tuberculosis isolate, 201, 203, 204
freezing and thawing, effect on infectivity, 203–204
human-type bacilli (H37Rv), 201, 202, 203, 204
overview, 200–201
Tubercles
alveolar macrophage role in establishment of grossly visible primary tubercles, 200
Tubercles (Continued)
definition, 436
development in humans, 197
in rabbits caused by inhaled BCG, 233–234
reactivation of healing pulmonary tubercles by glucocorticoids, 279–280
Tuberculin reactions
cytokines in, 312–323
microvasculature of lesions
histopathology, 164, 167
production of developing and healing lesions, 161–162
mononuclear cell activation in, 192–193
in rabbits, 358
Tuberculin sensitivity; see also Delayed-type hypersensitivity (DTH)
cavity formation in rabbits and, 78–79
disease control and, 346
in laboratory animals, 262
Tuberculin skin test
anergy, 105
booster phenomenon in repeated testing, 105–106
early positives, 38
size of reaction, prognostic value of, 105
Tuberculin traps, 185
Tuberculin unit, 99
Tuberculous lesions, 155–210; see also Pathogenesis
arrested, 28, 37, 38, 60–62
CMI and DTH required for, 101–102
early in humans, 263
inapparent, 60–62
Lurie's pulmonary lesion-count method, 196–210
lymphatics in, 144–145
macrophages, 177–194
activation, 189, 191
division, 189, 191
in vitro division of activated in BCG lesions, 179
in vitro [3H]Tdr labeling, 178–179
in vivo [3H]Tdr labeling, 180
overview, 178
turnover in healing dermal BCG lesions, 189, 191
turnover in mouse tuberculous granulomas, 193
microvascular density, 161–168
angiogenesis, regulators of, 167
blood supply, pathophysiology of, 167–168
capillary density, determination of, 162–163
histopathology of microvascular-cell interactions, 163–167
overview, 161
production of BCG lesions and tuberculin reactions, 161–162
produced by live and dead bacilli, comparisons of, 378
pulmonary lesions in rabbits, early, 170–175
macrophages, activation and division of bloodborne, 170–175
macrophages, division of activated pulmonary alveolar, 175
production by intravenous injection of bacilli, advantages of, 170
resistance to establishment in Lurie's rabbits
bovine-type bacilli, 216–218
human-type bacilli, 223–224
structural components, 155–159
caseous tissues, 155–157
granulation tissue, 155
healing, 158
liquefied caseum and cavities, 157–158
organ and species resistance, 158–159
overview, 155
persisting viable bacilli, 158
vascular adhesion molecules in, 327–336
activation of microvascular endothelium and caseous necrosis, 334–335
in acute inflammatory lesions, 331
in epithelioid cells, 333
functions, 333–334
identification of microvessels in tissue sections of BCG lesions, 329
leukocyte ligands in BCG lesions, 333
overview in, 328–329
in primary BCG lesions, 329–330
quantitation in tissue sections, 329
questions to be answered, 335–336
in reinfection BCG lesions, 331, 332
Tumor necrosis factor alpha (TNF-α), 99, 141, 304–308, 320–321, 323, 436
Types of human disease, 9–11
adult-type tuberculosis, 11, 12, 13, 14, 15
childhood-type tuberculosis, 8, 9–11
Types of human pulmonary tuberculosis, 9–11, 34–62
adult-type tuberculosis, 11, 12, 13, 14, 15, 51–52
advanced fibrocoseous, 46–47
cavitary lesions, analyses of, 59
childhood-type tuberculosis, 8, 9–11, 49–51
early primary lesion, 38
encapsulated caseous or calcified nodules, 38
establishment of infection, 35–38
exudative lesions, 39
in immunocompromised host, 59–60
inapparent lesions, 60–62
liquefied caseous lesions, 42–46
miliary, 39–42
multidrug-resistant bacilli, 57–59
pneumonia and pleurisy, 47–49
progressive, locally destructive lesions, 46
proliferative lesions, 38–39
subapical localization, 51–57
table, 35
U
Uric acid, 24
UV (ultraviolet) lights, for disease prevention, 18–19
V
Vaccine, 341–350
BCG
- combination vaccines, 349
- inapparent lesions and, 61–62
- in mice and guinea pigs, 343–344
- in monkeys, 258, 260
- nonspecific irritants, effect on, 193
- recombinant technology improved, 349
- strong CMI and weak DTH, 344–345
- systemic nature in humans, 360–361
- composition of improved
  - adjuvant composition, 345–346
  - antigen composition, 345
- degree of immunization produced, tubercle-count method for determining, 204
- DNA vaccines, 349
- efficacy
  - in aerosol infections versus intravenous infections, comparison of, 207
- BCG in New Zealand White rabbits, 363
- M. microti in New Zealand White rabbits, 363
- standardization for comparing relative, 346–347
- future possibilities, 349–350
- intradermal BCG in Lurie’s inbred rabbit strains lesions, 361
- protection, amount of, 361–363
- vaccine, 361
- intradermal in Lurie’s inbred rabbit strains, 361–363
- M. tuberculosis mutants, 349
- maximal effectiveness
  - factors influencing, 348
  - in humans, 347–348
  - in rabbits, 347–348
- mice and guinea pigs, immunization of, 343–344
- postinfection immunization, 349
- pulmonary tubercle establishment, effects on
  - macroscopic tubercle, 342–343
  - microscopic tubercle, 342
- recombinant technology improved vaccines, 349
- research, suggested future, 380
- reviews of possible new, 349–350
- routes of administration, 343
- systemic nature of BCG vaccination in humans, 360–361
- van Willebrand factor, 436
- van Zutphen rabbits, 241

Vascular adhesion molecules, 327–336
- activation of microvascular endothelium and caseous necrosis, 334–335
- in acute inflammatory lesions, 331
- in epithelioid cells, 333
- functions, 333–334
- identification of microvessels in tissue sections of BCG lesions, 329
- leukocyte ligands in BCG lesions, 333
- overview in, 328–329
- in primary BCG lesions, 329–330
- quantitation in tissue sections, 329
- questions to be answered, 335–336
- in reinfection BCG lesions, 331, 332
- Vascular endothelial growth factor (VEGF), 436
- Vascular thrombosis, role in caseous necrosis and inhibition of bacillary growth, 375–376
- VCAM-1 (vascular cell adhesion molecule-1), 327–333, 436
- VEGF (vascular endothelial growth factor), 436
- Virulence
  - of bacillary strain, 13–15, 24, 207
  - inhaled bacilli in rabbits, mice, and guinea pigs, 260–261
  - tubercle-count method, determination by bovine-type bacilli, 201
  - clinical Mycobacterium tuberculosis isolate, 201, 203, 204
  - freezing and thawing, effect on infectivity, 203–204
  - human-type bacilli (H37Rv), 201, 202, 203, 204
  - overview, 200–201
- VLA-4, 333

W
- Whole-body irradiation, see X-irradiation

X
- X-irradiation, 292–298
  - alveolar macrophage from granulomatous lungs, effects on, 294–296
  - dermal BCG lesions, effects on, 293
  - inhalation of virulent human-type bacilli, effects on, 296–297
  - lethal dose, 293
  - public health consequences of medical radiation, 297–298
  - pulmonary alveolar macrophage populations, effects on, 293–294
  - in rabbits, 297
  - recovery from effects of, 296