

Principles of Immunological Diagnosis in Medicine

F. MILGRÖM, M.D.

C. J. ABEYOUNIS, Ph.D.

K. KANO, M.D.

Principles of Immunological Diagnosis in Medicine

F. MILGROM, M.D.

Professor and Chairman

C. J. ABEYOUNIS, Ph.D.

Professor

K. KANO, M.D.

Professor

Department of Microbiology

School of Medicine

State University of New York at Buffalo



LEA & FEBIGER

Philadelphia • 1981

Lea & Febiger
600 Washington Square
Philadelphia, PA 19106

Library of Congress Cataloging in Publication Data

Main entry under title:

Principles of immunological diagnosis in medicine.

Bibliography.

Includes index.

1. Immunodiagnosis. I. Milgrom, Felix.
II. Abeyounis, C. John. III. Kano, Kyoichi. [DNLM:
1. Immunologic technics. 2. Serodiagnosis.
3. Bacterial infections—Diagnosis. 4. Virus
diseases—Diagnosis. 5. Immunologic diseases—Diagnosis.
QY250 P958]
RB46.5.P74
ISBN 0-8121-0720-9

80-20724

Copyright © 1981 by Lea & Febiger. Copyright under the International Copyright Union. All rights reserved. This book is protected by copyright. *No part of it may be reproduced in any manner or by any means without written permission from the publisher.*

Published in Great Britain by Henry Kimpton Publishers, London

PRINTED IN THE UNITED STATES OF AMERICA

Print No. 3 2 1

Preface

Immunodiagnosis was initiated at the end of the nineteenth and the beginning of the twentieth centuries when several serologic procedures were established and when the specificity of the antigen-antibody reaction was clearly recognized.

Most immunodiagnostic tests have been based on the detection of antibodies in sera of patients suffering or recovering from infectious diseases. Antigenic preparations of the causative agent of the given disease have been employed as reagents to detect the antibodies in the patient's serum, as exemplified by the first serodiagnostic test to be described, the Widal test for typhoid fever. In a few instances, however, antibodies have been found which have undeniable diagnostic significance even though they combine with an antigen apparently unrelated to the causative agent of the disease. In some infectious diseases, detection of delayed hypersensitivity reactions to microbial antigens serves better the diagnostic purpose than detection of humoral antibodies.

Diagnosis of an infectious disease may be occasionally facilitated by identification of the microbial antigen in the pathological specimen by means of a proper immune serum, e.g., detection of pneumococcal polysaccharides in pleural effusion in the course of pneumonitis.

The expanding vista of immunology has created many new immunodiagnostic

tests, the application of which has considerable practical value. Antisera have been employed for identification of species origin of various proteins, a principle of considerable importance for forensic medicine. Antisera have been used for detection of polymorphism within human species, and these tests resulted in discoveries of blood groups, histocompatibility antigens, and serum allotypes. Matching for transfusion and organ grafts is accomplished by immunodiagnostic procedures. Antisera have been used as reagents for quantitation of many hormones, and detection of chorionic gonadotropin has served as a basis for the diagnosis of pregnancy. The use of antisera for detection and quantitation of various serum components is the basis for diagnosis of hypogammaglobulinemias, myelomas, macroglobulinemias, and complement deficiencies.

Hypersensitivity reactions of the immediate type have been diagnosed for over half a century, but only recently were tests for identifying the insulting agent *in vitro* developed. Abnormalities of the immunological apparatus may lead to self-destruction in which the patient's immune response inflicts damage to his own tissues. Immunodiagnosis of many such diseases is established.

Progress in research on cellular immunity in the last few years brought new tests which become more and more valuable in

everyday practice for assessing the immunological responsiveness of the patients. Also, diseases caused by cellular hypersensitivity can be reliably tested by *in vitro* procedures.

The mushrooming of immunodiagnostic tests frequently brings a great deal of confusion in medical practice. The purpose of this book is to present the principles of most immunodiagnostic tests to a practitioner who finds it difficult to keep abreast of new developments. No attempt has been made to elaborate on any practical details of the tests. On the other hand, interpretation of the results as they are re-

ceived from the laboratory is discussed in some detail. Sources of errors and misinterpretation are pointed out whenever feasible. We are aware that there are excellent textbooks of immunology and of immunological procedures. This book does not belong to either of these two categories; however, we hope that it will fill the gap between them.

Felix Milgrom, M.D.
C. John Abeyounis, Ph.D.
Kyoichi Kano, M.D.

Buffalo, New York

Contributors

Abeyounis, C. John, Ph.D.

*Professor of Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Albini, Boris, M.D.

*Associate Professor of Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Allen, James C., M.D.

*Professor of Medicine
School of Medicine and
University Hospital
The University of Maryland
Baltimore, Maryland*

Andres, Giuseppe A.

*Professor of Microbiology, Pathology, and
Medicine
School of Medicine
State University of New York at Buffalo
Director
Renal Immunopathology Laboratory
The Buffalo General Hospital
Buffalo, New York*

Apicella, Michael A., M.D.

*Professor of Medicine
Director, Division of Infectious Diseases
School of Medicine
University of Nevada
Reno, Nevada*

Barron, Almen L., Ph.D.

*Professor and Chairman
Department of Microbiology and
Immunology
College of Medicine
University of Arkansas for Medical
Sciences
Little Rock, Arkansas*

Beutner, Ernst H., Ph.D.

*Professor of Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Beutner, Karl R., Ph.D., M.D.

*Assistant Instructor of Pediatrics
School of Nursing
University of California at Los Angeles
Los Angeles, California*

Brentjens, Jan R., M.D.

*Associate Professor of Pathology and
Microbiology
Research Associate Professor of Medicine
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Calkins, Evan, M.D.

*Professor of Medicine
School of Medicine
State University of New York at Buffalo
Head
Geriatrics Fellowship Program
Buffalo VA Medical Center
Buffalo, New York*

Chase, Merrill W., Ph.D.

*Professor Emeritus
Immunology and Microbiology
The Rockefeller University
New York, New York*

Chorzelski, Tadeusz P., M.D.

*Professor of Dermatology
Warsaw Academy of Medicine
Warsaw, Poland*

Collins, Arlene R., Ph.D.

*Associate Professor of Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Costaris, Arthur W.

*Senior Scientist
Ortho Diagnostics Inc.
Raritan, New Jersey*

Cox, Herald R., Sc.D.

*Research Professor Emeritus of
Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Cunningham, Roger K., Ph.D.

*Associate Professor of Microbiology
Department of Microbiology and The
Ernest Witebsky Center for Immunology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Deibel, Rudolf, M.D.

*Professor for Pediatrics and Microbiology
Albany Medical College
Division of Laboratories and Research
New York State Department of Health
Albany, New York*

Dowdle, Walter R., Ph.D.

*Assistant Director for Science
Center for Disease Control
Atlanta, Georgia*

Downing, Judith, Ph.D.

*Associate Professor of Biology
Bloomsburg State College
Bloomsburg, Pennsylvania*

Downs, Wilbur G., M.D., M.P.H.

*Clinical Professor of Epidemiology
Department of Epidemiology and Public
Health
School of Medicine
Yale University
Yale Arbovirus Research Unit
New Haven, Connecticut*

Emmett, Edward A., M.D.

*Professor of Environmental Health Sciences
Director, Division of Occupational Medicine
Johns Hopkins School of Hygiene
and Public Health
Baltimore, Maryland*

Ferrieri, Patricia, M.D.

*Professor of Pediatrics
University of Minnesota Medical School
Minneapolis, Minnesota*

Flanagan, Thomas D., Ph.D.

*Professor of Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Gallagher, Marie R., Ph.D.

*Research Assistant Professor of Pediatrics
and Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Herrmann, Kenneth L., M.D.

*Chief
Perinatal Virology Branch
Bureau of Laboratories
Center for Disease Control
Atlanta, Georgia*

Howell, Clifford Lee, M.D., P.H.

*Director of Virology
Alta Bates Hospital Clinical Laboratories
Berkeley, California*

Jablonska, Stefania, M.D.

*Professor and Chairman of Dermatology
Warsaw Academy of Medicine
Warsaw, Poland*

Kagan, Irving G., M.D.

*Director
Parasitology Division
Center for Disease Control
Atlanta, Georgia*

Kano, Kyoichi, M.D.

*Professor of Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Kaplan, Melvin H., M.D.

*Professor of Medicine
Director of Division of Rheumatology
and Immunology
University of Massachusetts
Medical School
Chief, Section Immunology
Department of Laboratory Medicine
University of Massachusetts Hospital
Worcester, Massachusetts*

Kendal, Alan P., Ph.D.

*Chief, Influenza Laboratory
Virology Division
Bureau of Laboratories
Center for Disease Control
Atlanta, Georgia*

Kite, Joseph H., Jr., Ph.D.

*Professor of Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Kumar, Vijay, Ph.D.

*Clinical Assistant Professor of Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Lambert, Paul H., M.D.

*Assistant Professor of Medicine
University of Geneva
Head
WHO Immunology Research and
Training Centre
Centre de Transfusion
Hôpital Cantonal
Geneva, Switzerland*

Lambert, Reginald M., Ph.D.

*Professor of Microbiology
School of Medicine
State University of New York at Buffalo
Director, Buffalo Region
American Red Cross Blood Services
Buffalo, New York*

Leddy, John P., M.D.

*Professor of Medicine and Microbiology
University of Rochester Medical Center
Chief, Clinical Immunology Unit
University of Rochester Medical Center
Rochester, New York*

Loghem, Erna van, Ph.D.

*Chief of the Department for Genetics of
Immunoglobulins
Central Laboratory of the Netherlands Red
Cross Blood Transfusion Service
Laboratory of Experimental and Clinical
Immunology
University of Amsterdam
Amsterdam, The Netherlands*

Mackay, Ian R., M.D.

*Head of the Clinical Research Unit
The Walter and Eliza Hall Institute
of Medical Research
Royal Melbourne Hospital
Victoria, Australia*

Márquez, Ernest D., Ph.D.

*Associate Professor of Microbiology
The M. S. Hershey Medical Center
The Pennsylvania State University
College of Medicine
Hershey, Pennsylvania*

Martin, William J.

*Professor of Pathology and Microbiology
and Immunology
School of Medicine
University of California at Los Angeles
Head, Section of Microbiology
Clinical Laboratories
UCLA Hospital and Clinics
Los Angeles, California*

Melnick, Joseph L., Ph.D.

*Distinguished Service Professor of
Virology and Epidemiology
Chairman, Department of Virology and
Epidemiology
Baylor College of Medicine
Houston, Texas*

Middlebrook, Gardner, M.D.

*Professor of Pathology
University of Maryland School of
Medicine
Baltimore, Maryland*

Milgrom, Felix, M.D.

*Professor and Chairman
Department of Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Neter, Erwin, M.D.

*Professor Emeritus of Pediatrics
and Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Noble, Bernice, Ph.D.

*Assistant Professor of Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Noble, Gary R., M.D.

*Chief, Respiratory Virology Branch
Virology Division
Bureau of Laboratories
Center for Disease Control
Atlanta, Georgia*

Nusbacher, Jacob, M.D.

*Associate Professor of Medicine
University of Rochester School of Medicine
and Dentistry
Rochester, New York*

O'Connell, Cornelius J., M.D., F.A.C.P.

*Associate Clinical Professor of
Microbiology and Medicine
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Ogra, Pearay L., M.D.

*Professor of Pediatrics and Microbiology
School of Medicine
State University of New York at Buffalo
Director, Division of Infectious Diseases
Children's Hospital
Buffalo, New York*

Oss, Carel J. van, Ph.D.

*Professor of Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Park, Byung H., M.D., M.S.

*Professor of Pediatrics and Microbiology
School of Medicine
State University of New York at Buffalo
Director
Immunobiology Laboratory
Children's Hospital of Buffalo
Buffalo, New York*

Penner, Edward, M.D.

*Clinical Assistant Professor
Second Department of Gastroenterology
University of Vienna Medical School
Vienna, Austria*

Rapp, Fred, Ph.D.

*Professor and Chairman
Department of Microbiology
The M. S. Hershey Medical Center
The Pennsylvania State University College
of Medicine
Hershey, Pennsylvania*

Reggiardo, Zulema, Ph.D.

*Associate Professor of Pathology
University of Maryland School of Medicine
Baltimore, Maryland*

Reichlin, Morris, M.D.

*Professor of Medicine and Biochemistry
School of Medicine
State University of New York at Buffalo
Chief, Clinical Immunology
Veterans Administration Medical Center
Buffalo, New York*

Reisman, Robert E., M.D.

*Clinical Professor of Medicine and
Pediatrics
School of Medicine
State University of New York at Buffalo
Buffalo, New York*

Reiss, Alice M., Ph.D.

*Director, Technical Applications
Laboratory
Ortho Diagnostics Inc.
Raritan, New Jersey*

Rocklin, Ross E., M.D.

*Associate Professor of Medicine
Tufts University School of Medicine
Chief, Allergy Division
New England Medical Center Hospital
Boston, Massachusetts*

Rosenfeld, Stephen I., M.D.

*Associate Professor of Medicine
University of Rochester Medical Center
Rochester, New York*

Sepulveda, Marion, M.A.

*Supervisor of Immunopathology
Buffalo General Hospital
Buffalo, New York*

Targowski, Stanislaw P., D.V.M., Ph.D.

*Associate Professor of Veterinary
Preventive Medicine
College of Veterinary Medicine
The Ohio State University
Columbus, Ohio*

Walls, Kenneth W., M.D.

*Chief, Parasitic Serology Branch
Parasitology Division
Center for Disease Control
Atlanta, Georgia*

Wheat, L. Joseph, M.D.

*Associate Professor of Medicine
Indiana University School of Medicine
Indianapolis, Indiana*

White, Arthur, M.D.

*Professor of Medicine
Indiana University School of Medicine
Chief of Infectious Diseases
Indiana University Medical Center
Indianapolis, Indiana*

Wicher, Konrad, D.M.Sc., Ph.D.

*Professor of Microbiology
School of Medicine
State University of New York at Buffalo
Buffalo, New York
Director for Clinical Microbiology and
Immunology Laboratories
Division of Laboratories and Research
New York State Department of Health
Albany, New York*

Wick, Georg, M.D.

*Professor and Chairman
Institute for General and Experimental
Pathology
University of Innsbruck
Innsbruck, Austria*

Wright, John R., M.D.

*Professor and Chairman
Department of Pathology
School of Medicine
State University of New York at Buffalo
Head, Department of Pathology
Buffalo General Hospital
Buffalo, New York*

Contents

SECTION I. Basic Principles

| | |
|--|----|
| 1. Immune Responses in Man Felix Milgrom and C. John Abeyounis | 3 |
| 2. Phagocytosis Byung H. Park | 9 |
| 3. Antigens and Antibodies Carel J. van Oss | 14 |
| 4. <i>In Vitro</i> Tests for Cell-Mediated Immunity Ross E. Rocklin | 28 |
| 5. Skin Tests Merrill W. Chase | 36 |
| 6. Principles of Immunodiagnosis Felix Milgrom and Kyoichi Kano | 41 |

SECTION II. Diseases Elicited by Bacteria and Fungi

| | |
|--|----|
| 7. Staphylococcus L. Joseph Wheat and Arthur White | 49 |
| 8. Streptococcus Patricia Ferrieri | 54 |
| 9. Neisseria Michael A. Apicella | 61 |
| 10. Bacillus Cornelius J. O'Connell | 64 |
| 11. Clostridium Clifford Lee Howell and William J. Martin | 67 |
| 12. Corynebacterium Felix Milgrom and Kyoichi Kano | 71 |
| 13. Listeria C. John Abeyounis | 76 |
| 14. Enterobacteriaceae Erwin Neter | 78 |
| 15. Yersinia Pestis Konrad Wicher | 87 |

| | |
|--|-----|
| 16. <i>Vibrio Cholerae</i> | |
| Erwin Neter | 90 |
| 17. <i>Pseudomonas Aeruginosa</i> | |
| Erwin Neter | 92 |
| 18. <i>Pseudomonas Mallei</i> | |
| Stanislaw P. Targowski | 93 |
| 19. <i>Legionella Pneumophila</i> | |
| Erwin Neter | 96 |
| 20. <i>Brucella</i> | |
| Konrad Wicher | 97 |
| 21. <i>Francisella</i> | |
| Konrad Wicher | 102 |
| 22. <i>Haemophilus</i> | |
| Konrad Wicher | 105 |
| 23. <i>Bordetella</i> | |
| Konrad Wicher | 108 |
| 24. <i>Bacteroides and Fusobacterium</i> | |
| Roger K. Cunningham | 111 |
| 25. <i>Mycobacterium</i> | |
| Gardner Middlebrook and Zulema Reggiardo | 114 |
| 26. <i>Actinomyces</i> | |
| Roger K. Cunningham and Judith Downing | 123 |
| 27. <i>Treponema</i> | |
| Felix Milgrom | 126 |
| 28. <i>Borrelia</i> | |
| Felix Milgrom | 134 |
| 29. <i>Leptospira</i> | |
| Felix Milgrom | 136 |
| 30. <i>Mycoplasma</i> | |
| Joseph H. Kite, Jr. | 139 |
| 31. Pathogenic Fungi | |
| Joseph H. Kite, Jr. | 145 |

SECTION III. Diseases Elicited by Rickettsiae and Chlamydiae

| | |
|---------------------------|-----|
| 32. <i>Rickettsia</i> | |
| Herald R. Cox | 165 |
| 33. <i>Chlamydia</i> | |
| Almen L. Barron | 183 |

SECTION IV. Diseases Elicited by Viruses

| | |
|--|-----|
| 34. Influenza, Parainfluenza, and Respiratory Syncytial Viruses | |
| Walter R. Dowdle, Gary R. Noble, and Alan P. Kendal | 195 |
| 35. Herpesviruses | |
| Ernest D. Márquez and Fred Rapp | 204 |
| 36. Heterophile Reactions in Infectious Mononucleosis | |
| Kyoichi Kano | 211 |

| | |
|---|-----|
| 37. Enteroviruses | |
| Joseph L. Melnick | 213 |
| 38. Rubella Virus | |
| Kenneth L. Herrmann | 223 |
| 39. Measles and Mumps Viruses | |
| Thomas D. Flanagan | 230 |
| 40. Arboviruses | |
| Wilbur G. Downs | 235 |
| 41. Adenoviruses | |
| Rudolf Deibel | 243 |
| 42. Hepatitis Viruses | |
| Pearay L. Ogra and Karl R. Beutner | 247 |
| 43. Rabies Virus | |
| Thomas D. Flanagan | 260 |
| 44. Coronaviruses | |
| Thomas D. Flanagan | 262 |
| 45. Rotaviruses | |
| Thomas D. Flanagan and Marie R. Gallagher | 264 |
| 46. Vaccinia and Variola Viruses | |
| Thomas D. Flanagan | 266 |
| 47. Arenaviruses, Marburg and Ebola Agents | |
| Arlene Collins | 268 |

SECTION V. Diseases Elicited by Animal Parasites

| | |
|--|-----|
| 48. Protozoa and Helminths | |
| Irving G. Kagan and Kenneth W. Walls | 275 |

SECTION VI. Immunological Disorders

| | |
|---|-----|
| 49. Immunoglobulin Abnormalities | |
| James C. Allen | 289 |
| 50. Complement and Its Alterations in Disease | |
| John P. Leddy and Stephen I. Rosenfeld | 296 |
| 51. Deficiencies in Cell-Mediated Immunity | |
| Byung H. Park | 303 |
| 52. Immune Complex Diseases | |
| Paul H. Lambert | 310 |
| 53. Atopic Diseases | |
| Robert E. Reisman | 318 |
| 54. Contact Dermatitis | |
| Edward A. Emmett | 326 |
| 55. Systemic Lupus Erythematosus | |
| Morris Reichlin | 331 |
| 56. Rheumatoid Arthritis | |
| Felix Milgrom | 337 |
| 57. Amyloidosis | |
| Evan Calkins and John R. Wright | 341 |

| | |
|---|------------|
| 58. Immune Hemolytic Anemia and Immune Thrombocytopenic Purpura John P. Leddy and Jacob Nusbacher | 347 |
| 59. Thyroiditis Joseph H. Kite, Jr. | 353 |
| 60. Adrenatitis, Idiopathic Hypoparathyroidism, and Diabetes Mellitus Georg Wick and Boris Albini | 359 |
| 61. Infertility Boris Albini and Bernice Noble | 366 |
| 62. Myasthenia Gravis Boris Albini and Georg Wick | 372 |
| 63. Serum Sickness Boris Albini | 375 |
| 64. Heart Diseases Melvin H. Kaplan | 380 |
| 65. Kidney Diseases Jan R. Brentjens, Marion Sepulveda, and Giuseppe A. Andres | 385 |
| 66. Liver Diseases Ian R. Mackay | 393 |
| 67. Gastrointestinal Tract Diseases Edward Penner and Boris Albini | 398 |
| 68. Bullous Diseases Ernst H. Beutner, Tadeusz P. Chorzelski, Stefania Jablonska, and Vijay Kumar | 405 |
| SECTION VII. Identification of Normal and Pathological Tissue Antigens | |
| 69. Blood Groups and Transfusion Reginald M. Lambert | 413 |
| 70. Histocompatibility and Transplantation Kyoichi Kano | 421 |
| 71. Allotypes Erna van Loghem | 427 |
| 72. Hormones Alice M. Reiss and Arthur W. Costaris | 431 |
| 73. C-Reactive Protein Edward Penner | 448 |
| 74. Malignancies C. John Abeyounis | 450 |
| 75. Forensic Medicine Felix Milgrom | 456 |
| Summary | 461 |
| Index | 505 |

Section I

BASIC PRINCIPLES

1

Immune Responses in Man

FELIX MILGROM and C. JOHN ABEYOUNIS

Man and animals are endowed with natural or innate resistance to infectious disease that is present from birth and is frequently considered the first line of defense against microbial invasion. Undoubtedly the most important organ providing natural resistance is the skin, which acts as a mechanical barrier. Acidity of the sweat, gastric juice, and urine also has antimicrobial action. Secretions contain antibacterial substances such as lysozyme. If a microorganism passes these superficial defense lines and enters deeper layers of tissue, it encounters a number of antibacterial factors that can be demonstrated in normal human sera. Finally, phagocytic cells, polymorphonuclear leukocytes of the circulation, and macrophages of the tissues present further resistance to the invader.

In addition to these "nonspecific," physiological defense mechanisms, resistance may be acquired from the contact with a given microorganism. This contact initiates a host response that establishes a resistance that is specifically directed against this organism. These specific defense mechanisms are discussed under the term *immunity*, which denotes specific protection and stems from the Latin adjective *immunis*, meaning "free from duty, protected." Induction of the immune response involves the participation of both macrophages and lymphocytes. The response may be manifested or exerted in two forms: (1) humoral, in which the effector cells are B lymphocytes, i.e., lymphocytes that, in the

avian species, mature in the bursa of Fabricius and, in mammals, mature in an as yet unidentified counterpart of the bursa, and (2) cellular, in which the effector cells are T lymphocytes, i.e., lymphocytes that mature in the thymus.

It has been known from antiquity that recovery from an infectious disease is followed by immunity to that particular disease, but not to any other malady. In the last decade of the nineteenth century, several important observations were made that related this immunity to substances in the blood serum.

HUMORAL IMMUNITY

Von Behring and Kitasato showed that the serum of animals injected with sublethal doses of tetanus or diphtheria toxin neutralizes the corresponding toxin. This phenomenon was called *toxin neutralization*, and serum substances accomplishing this were termed *antitoxins*. Antitoxins appear as a result of infection with a toxin-producing organism or injection of a toxin, and they show specificity of reaction with the toxin that engendered their formation.

Pfeiffer injected killed cultures of cholera organisms into guinea pigs and showed that blood serum and body fluids of these animals dissolved cholera organisms *in vitro*. This phenomenon was called *lysis*, more specifically, *bacteriolysis*, and the substances accomplishing this were named *lysins*, more specifically, *bacteriolysins*. Pfeiffer also performed *in vivo* exper-