THE HARVEY LECTURES

Delivered under the auspices of

THE HARVEY SOCIETY OF NEW YORK

Previously Published

FIRST SERIES . . . 1905-1906
SECOND SERIES . . 1906-1907
THIRD SERIES . . 1907-1908
FOURTH SERIES . . 1908-1909
FIFTH SERIES . . 1909-1910
SIXTH SERIES . . 1910-1911
SEVENTH SERIES . 1911-1912
EIGHTH SERIES . . 1912-1913
NINTH SERIES . . 1913-1914

"The Harvey Society deserves the thanks of the profession at large for having organized such a series and for having made it possible for all medical readers to share the profits of the undertaking."

—*Medical Record, New York.*

Crown 8vo. Cloth, $2.00 net, per volume.

J. B. LIPPINCOTT COMPANY

Publishers Philadelphia

Digitized by Google

THE HARVEY LECTURES

DELIVERED UNDER THE AUSPICES OF

THE HARVEY SOCIETY OF NEW YORK

1913-1914

BY

PROF. AUGUSTUS D. WALLER
PROF. ADOLF SCHMIDT
DR. CHARLES V. CHAPIN
PROF. G. H. PARKER
DR. RUFUS COLE
PROF. VICTOR C. VAUGHAN
PROF. SVEN G. HEDIN
PROF. J. J. R. MACLEOD
PROF. RICHARD P. STRONG
PROF. WILLIAM STEWART HALSTED

PHILADELPHIA AND LONDON
J. B. LIPPINCOTT COMPANY

Digitized by Google

HARVARD UNIVERSITY
SCHOOL OF MEDICINE AND PUBLIC HEALTH
LIBRARY

1.E.1906.1

Copyright, 1915
By J. B. Lippincott Company

Digitized by Google

PREFACE

An apology is due our readers for the late appearance of this, the ninth volume of Harvey Lectures. For this delay in publication full responsibility must fall on the undersigned, who assumed the duties of editor on account of the absence in Europe of the Secretary, Dr. John A. Mandel.

We wish to express, as in former years, obligations for permission to reprint those lectures which have already appeared in medical and scientific journals: To the editors of Science, The Archives of Internal Medicine, and the American Journal of Medical Sciences for allowing us to republish, respectively, the lectures by Prof. Parker, Dr. Cole, and Prof. Schmidt.

April, 1915. Robert A. Lambert, *Acting Secretary.*

Digitized by Google

Digitized by Google

THE HARVEY SOCIETY

A SOCIETY FOR THE DIFFUSION OF KNOWLEDGE OF THE MEDICAL SCIENCES

CONSTITUTION

I.

This Society shall be named the Harvey Society.

II.

The object of this Society shall be the diffusion of scientific knowledge in selected chapters in anatomy, physiology, pathology, bacteriology, pharmacology, and physiological and pathological chemistry, through the medium of public lectures by men who are workers in the subjects presented.

III.

The members of the Society shall constitute three classes: Active, Associate, and Honorary members. Active members shall be laboratory workers in the medical or biological sciences residing in the City of New York. Associate members shall be such other persons as are in sympathy with the objects of the Society. Honorary members shall be those who have delivered lectures before the Society and who are neither active nor associate members. Associate and honorary members shall not be eligible to office, nor shall they be entitled to a vote.

Members shall be elected by ballot. They shall be nominated to the Executive Committee and the names of the nominees shall accompany the notice of the meeting at which the vote for their election will be taken.

Digitized by Google

IV.

The management of the Society shall be vested in an executive committee, to consist of a President, a Vice-President, a Secretary, a Treasurer, and three other members, these officers to be elected by ballot at each annual meeting of the Society to serve one year.

V.

The Annual meeting of the Society shall be held soon after the concluding lecture of the course given during the year, at a time and place to be determined by the Executive Committee. Special meetings may be held at such times and places as the Executive Committee may determine. At all the meetings *ten* members shall constitute a quorum.

VI.

Changes in the Constitution may be made at any meeting of the Society by a majority vote of those present after previous notification of the members in writing.

Digitized by Google

OFFICERS AND MEMBERS OF THE SOCIETY

OFFICERS

William G. MacCallum, *President*
Rufus Cole, *Vice-President*
Edward K. Dunham, *Treasurer*
John A. Mandel, *Secretary*

EXECUTIVE COMMITTEE

Graham Lusk
Frederic S. Lee
Warfield T. Longcope
The Officers Ex-Officio

ACTIVE MEMBERSHIP

Dr. John S. Adriance
Dr. Hugh Auchincloss
Dr. John Auer
Dr. F. W. Bancroft
Dr. S. P. Beebe
Dr. S. R. Benedict
Dr. Herman M. Biggs
Dr. Harlow Brooks
Dr. Leo Buerger
Dr. Russell Burton-Optiz
Dr. E. E. Butterfield
Dr. Alexis Carrel
Dr. P. F. Clark
Dr. A. F. Coca
Dr. A. E. Cohn
Dr. Rufus Cole
Dr. H. D. Dakin
Dr. C. B. Davenport
Dr. A. R. Dochez
Dr. George Draper
Dr. E. F. Du Bois
Dr. E. K. Dunham
Dr. W. J. Elser
Dr. Haven Emerson
Dr. James Ewing
Dr. J. S. Ferguson
Dr. Cyrus W. Field
Dr. Simon Flexner
Dr. N. B. Foster
Dr. W. J. Gies
Dr. T. S. Githens
Dr. F. M. Hanes
Dr. T. W. Hastings
Dr. R. A. Hatcher
Dr. G. S. Huntington
Dr. Holmes C. Jackson
Dr. W. A. Jacobs
Dr. H. H. Janeway
Dr. T. C. Janeway
Dr. J. W. Jobling
Dr. D. R. Joseph
Dr. D. M. Kaplan
Dr. I. S. Kleiner
Dr. R. V. Lamar
Dr. R. A. Lambert
Dr. F. S. Lee
Dr. E. S. L'Esperance
Dr. P. A. Levene
Dr. I. Levin
Dr. E. Libman
Dr. C. C. Lieb
Dr. W. T. Longcope
Dr. Graham Lusk
Dr. F. H. McCrudden

Digitized by Google

ACTIVE MEMBERSHIP—*Continued*

Dr. W. G. MacCallum
Dr. W. J. MacNeal
Dr. A. R. Mandel
Dr. John A. Mandel
Dr. F. S. Mandlebaum
Dr. W. H. Manwaring, Jr.
Dr. S. J. Meltzer
Dr. Adolph Meyer
Dr. G. M. Meyer
Dr. L. S. Milne
Dr. H. O. Mosenthal
Dr. J. R. Murlin
Dr. Hideyo Noguchi
Dr. Charles Norris
Dr. Horst Oertel
Dr. Eugene L. Opie
Dr. B. S. Oppenheimer
Dr. Wm. H. Park
Dr. F. W Peabody
Dr. R. M. Pearce
Dr. F. H. Pike
Dr. T. M. Prudden
Dr. A. N. Richards
Dr. C. G. Robinson
Dr. Peyton Rous
Dr. Otto H. Schultze
Dr. E. L. Scott
Dr. H. D. Senior
Dr. C. R. Stockard
Dr. I. Strauss
Dr. H. F. Swift
Dr. B. T. Terry
Dr. J. C. Torrey
Dr. D. D. Van Slyke
Dr. Karl M. Vogel
Dr. Augustus Wadsworth
Dr. A. J. Wakeman
Dr. G. B. Wallace
Dr. Richard Weil
Dr. Wm. H. Welker
Dr. J. S. Wheelwright
Dr. C. G. Wiggers
Dr. Anna Williams
Dr. H. B. Williams
Dr. R. J. Wilson
Dr. Martha Wollstein
Dr. F. C. Wood
Dr. Jonathan Wright

ASSOCIATE MEMBERSHIP

Dr. Robert Abbe
Dr. C. F. Adams
Dr. I. Adler
Dr. F. H. Albee
Dr. W. B. Anderton
Dr. Wm. Armstrong
Dr. Gorham Bacon
Dr. Pearce Bailey
Dr. T. B. Barringer
Dr. Simon Baruch
Dr. W. A. Bastedo
Dr. Joseph A. Blake
Dr. George Blumer
Dr. A. Bookman
Dr. David Bovaird, Jr.
Dr. John Winters Brannan
Dr. J. Brettauer
Dr. George E. Brewer
Dr. Nathan E. Brill
Dr. William B. Brinsmade
Dr. E. B. Bronson
Dr. S. A. Brown
Dr. Jesse G. M. Bullowa
Dr. Glentworth R. Butler
Dr. C. N. B. Camac
Dr. Wm. F. Campbell

Digitized by Google

ASSOCIATE MEMBERSHIP—*Continued*

Dr. R. J. Carlisle
Dr. H. S. Carter
Dr. A. F. Chace
Dr. T. M. Cheeseman
Dr. Cornelius G. Coakley
Dr. H. C. Coe
Dr. Warren Coleman
Dr. Wm. B. Coley
Dr. C. F. Collins
Dr. Lewis A. Conner
Dr. Edwin B. Cragin
Dr. Floyd M. Crandall
Dr. G. W. Crary
Dr. Chas. L. Dana
Dr. Thomas Darlington
Dr. D. Bryson Delavan
Dr. Edward B. Dench
Dr. W. K. Draper
Dr. Alexander Duane
Dr. Theodore Dunham
Dr. Max Einhorn
Dr. Charles A. Elsberg
Dr. A. A. Epstein
Dr. Evan M. Evans
Dr. S. M. Evans
Dr. Edward D. Fisher
Dr. Rolfe Floyd
Dr. John A. Fordyce
Dr. Joseph Fraenkel
Dr. R. T. Frank
Dr. Rowland Godfrey Freeman
Dr. Wolff Freudenthal
Dr. Lewis F. Frissell
Dr. Virgil P. Gibney
Dr. Charles L. Gibson
Dr. J. Riddle Goffe
Dr. S. S. Goldwater
Dr. M. Goodridge
Dr. N. W. Green
Dr. J. C. Greenway
Dr. Graeme M. Hammond
Dr. T. Stewart Hart
Dr. John A. Hartwell
Dr. J. R. Hayden
Dr. Henry Heiman
Dr. A. F. Hess
Dr. August Hoch
Dr. A. W. Hollis
Dr. H. A. Houghton
Dr. Francis Huber
Dr. John H. Huddleston
Dr. Edward L. Hunt
Dr. Woods Hutchinson
Dr. Leopold Jaches
Dr. Abraham Jacobi
Dr. Geo. W. Jacoby
Dr. Ralph Jacoby
Dr. Walter B. James
Dr. S. E. Jelliffe
Dr. Frederick Kammerer
Dr. Ludwig Kast
Dr. Jacob Kaufmann
Dr. C. G. Kerley
Dr. P. D. Kerrison
Dr. E. L. Keyes, Jr.
Dr. Eleanor Kilham
Dr. Otto Kiliani
Dr. Arnold Knapp
Dr. Linnaues E. La Fetra
Dr. Alexander Lambert
Dr. S. W. Lambert
Dr. Gustav Langman
Dr. Boleslaw Lapowski
Dr. B. J. Lee
Dr. Robert Lewis, Jr.
Dr. Eli Long
Dr. William C. Lusk
Dr. H. H. M. Lyle
Dr. David H. McAlpin
Dr. J. F. McKernon

Digitized by Google

ASSOCIATE MEMBERSHIP—*Continued*

Dr. Morris Manges
Dr. George Mannheimer
Dr. Wilbur B. Marple
Dr. Frank S. Meara
Dr. Victor Meltzer
Dr. Walter Mendelson
Dr. Alfred Meyer
Dr. Willy Meyer
Dr. Michael Michailovsky
Dr. G. N. Miller
Dr. James A. Miller
Dr. A. V. Moschcowitz
Dr. John P. Munn
Dr. Archibald Murray
Dr. Van Horne Norrie
Dr. N. R. Norton
Dr. W. P. Northrup
Dr. Alfred T. Osgood
Dr. H. McM. Painter
Dr. Eleanor Parry
Dr. Stewart Paton
Dr. Henry S. Patterson
Dr. Chas. H. Peck
Dr. Frederick Peterson
Dr. Godfrey R. Pisek
Dr. William M. Polk
Dr. Sigismund Pollitzer
Dr. Nathaniel B. Potter
Dr. Wm. J. Pulley
Dr. Edward Quintard
Dr. A. F. Riggs
Dr. Andrew R. Robinson
Dr. John Rogers, Jr.
Dr. Joseph C. Roper
Dr. Julius Rudisch
Dr. Bernard Sachs
Dr. Thos. B. Satterthwaite
Dr. Reginald H. Sayre
Dr. Max G. Schlapp
Dr. E. W. Scripture
Dr. N. M. Shaffer
Dr. M. H. Sicard
Dr. H. M. Silver
Dr. William K. Simpson
Dr. A. Alexander Smith
Dr. F. P. Solley
Dr. F. E. Sondern
Dr. J. Bentley Squier, Jr.
Dr. N. Stadtmuller
Dr. Antonio Stella
Dr. Richard Stein
Dr. Abram R. Stern
Dr. George D. Stewart
Dr. L. A. Stimson
Dr. William S. Stone
Dr. George M. Swift
Dr. Parker Syms
Dr. A. S. Taylor
Dr. John S. Thacher
Dr. A. M. Thomas
Dr. Gilman Thompson
Dr. Wm. H. Thomson
Dr. S. W. Thurber
Dr. W. R. Townsend
Dr. Philip Van Ingen
Dr. J. D. Voorhees
Dr. H. F. Walker
Dr. John B. Walker
Dr. Josephine Walter
Dr. James Sears Waterman
Dr. R. W. Webster
Dr. John E. Weeks
Dr. Herbert B. Wilcox
Dr. Linsly R. Williams
Dr. W. R. Williams
Dr. Margaret B. Wilson
Dr. George Woolsey
Dr. John Van Doren Young
Dr. Hans Zinsser

Digitized by Google

HONORARY MEMBERSHIP

Prof. J. G. Adami
Prof. E. R. Baldwin
Prof. Lewellys F. Barker
Prof. F. G. Benedict
Prof. R. R. Bensley
Prof. T. G. Brodie
Prof. A. Calmette
Prof. W. E. Castle
Prof. W. B. Cannon
Prof. Chas. V. Chapin
Prof. Hans Chiari
Prof. R. H. Chittenden
Prof. Otto Cohnheim
Prof. Edward G. Conklin
Prof. W. T. Councilman
Prof. G. W. Crile
Prof. Harvey Cushing
Prof. Arthur R. Cushny
Prof. D. L. Edsall
Prof. Joseph Erlanger
Prof. William Falta
Prof. Otto Folin
Prof. Frederick P. Gay
Prof. W. S. Halsted
Prof. Ross G. Harrison
Prof. Sven G. Hedin
Prof. Ludwig Hektoen
Prof. L. J. Henderson
Prof. W. H. Howell
Prof. G. Karl Huber
Prof. Joseph Jastrow
Prof. H. S. Jennings
Prof. E. O. Jordan
Prof. E. P. Joslin
Prof. Franz Knoop
Prof. Albrecht Kossel
Prof. J. B. Leathes
Prof. A. Magnus-Levy
Prof. Thomas Lewis
Prof. Jacques Loeb
Prof. A. S. Loevenhart
Prof. A. B. MacCallum
Prof. J. J. R. MacLeod
Prof. F. B. Mallory
Prof. L. B. Mendel
Prof. Hans Meyer
Prof. Charles S. Minot
Prof. T. H. Morgan
Prof. Friedrich Muller
Prof. Karl von Noorden
Prof. Fred G. Novy
Prof. G. H. F. Nuttall
Prof. Henry Fairfield Osborn
Prof. T. B. Osborne
Prof. G. H. Parker
Prof. W. T. Porter
Prof. J. J. Putnam
Prof. T. W. Richards
Prof. Max Rubner
Major F. F. Russell
Prof. E. A. Schaefer
Prof. Adolph Schmidt
Prof. W. T. Sedgwick
Prof. Theobald Smith
Prof. E. H. Starling
Prof. G. N. Stewart
Prof. Richard P. Strong
Prof. A. E. Taylor
Prof. W. S. Thayer
Prof. Victor C. Vaughan
Prof. Max Verworn
Prof. A. D. Waller
Prof. J. Clarence Webster
Prof. H. Gideon Wells
Prof. E. B. Wilson
Sir Almroth Wright

Digitized by Google

Digitized by Google

CONTENTS

PAGE

A Short Account of the Origin and Scope of Electrocardiography..... 17
PROF. AUGUSTUS D. WALLER—University of London.

Severe Anæmia Connected With Gastro-Intestinal Diseases.......... 34
PROF. ADOLF SCHMIDT—University of Halle.

The Air as a Vehicle of Infection.................................... 47
DR. CHARLES V. CHAPIN—Health Department, Providence, R. I.

The Origin and Evolution of the Nervous System.................... 72
PROF. G. H. PARKER—Harvard University.

Pneumococcus Infection and Lobar Pneumonia...................... 85
DR. RUFUS COLE—Rockefeller Institute.

The Phenomena of Infection.. 132
PROF. VICTOR C. VAUGHAN—University of Michigan.

Colloidal Reactions and Their Relations to Biology................. 162
PROF. SVEN G. HEDIN—University of Upsala.

Recent Work on the Physiological Pathology of Glycosuria.......... 174
PROF. J. J. R. MACLEOD—Western Reserve University.

The Etiology of Oroya Fever and Verruga Peruviana................ 204
PROF. RICHARD P. STRONG—Harvard University.

The Significance of the Thymus Gland in Graves's Disease........... 224
PROF. WILLIAM STEWART HALSTED—Johns Hopkins University.

Digitized by Google

THE PHENOMENA OF INFECTION*

PROFESSOR VICTOR C. VAUGHAN
University of Michigan

DOERR of Vienna (Handbuch d. path. Mikroorganismen, Zweite Auflage) closes a most excellent review of recent work on so-called anaphylaxis or protein sensitization with the following paragraph:

> While it must be admitted that the action of those infective bacteria, which are not known to produce specific toxins, remains without explanation, and while the theories which have been developed by Von Pirquet, Friedberger, Vaughan, Schittenhelm, Weichardt and others have opened up a new way to the understanding of incubation, fever and crises, still it must be borne in mind that the premises of these theories do not possess the force of chemical facts. It has not been positively shown that the symptoms of anaphylaxis are due to the parenteral cleavage of proteins, that the true anaphylactic poison is identical with that produced *in vitro* and that both come from the antigen. Even if we agree with Dold, Sachs and Ritz that so far as the rôle of anaphylaxis in the infectious diseases is concerned, it is irrelevant from what matrix and by what processes the hypothetical anaphylactic poison is produced, even then all the difficulties are not removed. Numerous infecting agents are not anaphylactogens; they do not differ in their effects upon sensitized and non-sensitized animals and even when there are differences they are slight compared with those seen when the protein antigens derived from the higher plants and animals are employed. The relatively simple structure of the bacterial proteins is the cause of this. Therefore it is questionable whether one has the right to explain the phenomena of the infectious diseases with serum sensitization as a starting-point. Moreover, the infections are not so monomorphic as some suppose from a superficial consideration. Measles and scarlet fever seem much alike, still during an attack of the former the body cannot be sensitized to tuberculin or vaccine, while the latter does not induce this condition.

This statement, following as it does a fair but critical review of the new theories referred to and the work upon which

* Delivered January 17, 1914.

Digitized by Google

they rest, is certainly just. The purpose of this paper is to state the sensitization or parenteral digestion theory, as I understand it, and weigh the evidence for and against it. It should be plainly understood that in doing this I am speaking my own views and it is probable that no one of the investigators with whom Doerr has done me the honor of grouping me would agree with me in all details, nor I with them.

It may be well to meet at the outset the chief objection which Doerr makes, in the above quotation, to the sensitization theories. He states that the bacterial proteins have a relatively simple molecular structure. This is an assumption without a fact to support it. Because bacterial cells are relatively simple morphologically it has been inferred that they are simple in the chemical structure of their protein constituents. This certainly is not true. My students and I have shown that the bacterial proteins are quite as complex as those of the cells of our own bodies. They contain at least two carbohydrate groups, one of which has been quite positively located in the nucleic-acid fraction, while the seat of the other has not been determined. They furnish nuclein bases, thus showing the presence of one or more nucleic acids, as has been inferred from their behavior toward the basic stains. They yield diamino- and monoamino-acids in like abundance and variety as these are found in the proteins of the higher plants and animals. In short, bacteria consist largely of glyconucleo-proteins. Recent papers from Kossel's laboratory (Zeitschrift f. physiolog. Chemie, 1913, lxxxix, 85) confirm our claim that the chemical structure of the bacterial proteins is not simple.

Doerr's statement that numerous infective agents are not anaphylactogens is one which I can neither confirm nor deny. It seems to me, however, to be an assertion which needs qualification. There are many kinds and degrees of sensitization depending upon the sensitizer and the cell acted upon. In some instances the sensitized state continues for many years; in others it lasts for only a few weeks or months, while in still others it is even more ephemeral.

Digitized by Google

In order to save space and time I will formulate my views concerning the phenomena of infection as follows:

All infecting agents are living proteins capable of growth and multiplication. They may contain carbohydrates, fats and waxes, possibly other and simpler chemical bodies, but their essential and characteristic constituents are proteins. This is true not only of all infecting agents but of all life units. The infecting agents which we know are bacteria, protozoa, moulds and yeasts. These possess physical characters which enable us to individualize them, but theoretically there is no reason why a living thing, and consequently a virus, may not be a liquid. Each and every living thing must feed, assimilate and excrete. Its molecules must be in a labile state, taking in and casting out atomic groups simultaneously. The bacterium can feed only on the pabulum within its reach and of that it can utilize only that which it can fit into its molecular structure. Only this is pabulum to the cell. Organisms which cannot utilize the proteins of the animal's body cannot be pathogenic to that animal. All living things feed through the activity of their ferments. These are of two kinds, analytic and synthetic. The former split up the pabulum into proper building stones, while the latter place these stones in proper position in the cell molecule. Usually we say that cell ferments are extra- and intracellular. The former diffuse more or less into the medium and exert a cleavage action; the latter remain in the cell and do a constructive work. That these ferments are in reality different bodies is indicated not only by the parts they play in the life of the cell, but also by the fact that they are differently affected by heat and chemical agents. Ferments are specific in two senses; first, each kind of cell elaborates its own ferment; and second, the ferment is able to split up only certain proteins. Besides, for each ferment there is an optimum temperature at which its action is greatest. There are many bacteria which cannot grow at body temperature. These organisms cannot be pathogenic. This is true of most saprophytic bacteria found in water. Then, there is the relation between ferment and substrate which requires a nicety of adjustment which is not

Digitized by Google

thoroughly understood. Finally, in a general way an accumulation of fermentative products retards the action of the ferment.

It must be remembered that the body-cells, like the bacterial cells, digest proteins. They also elaborate analytic and synthetic, or extra- and intracellular ferments. These ferments have been especially studied in the leucocyte. The extracellular ferments elaborated in leucocytes are germicidal because they digest bacterial proteins, and they are destroyed by a temperature of 56°. The intracellular ferments of the leucocyte are also bactericidal and for a like reason, but they bear a much higher temperature. Every living cell in the animal body, like every bacterial cell, elaborates its specific ferments. This has been positively demonstrated by Abderhalden and his students (Zeitschrift f. physiolog. Chemie, 1913, lxxxvii, 220, 231).

It must be evident from what has been said that the pathogenicity of a given virus is determined by its ability or inability to grow in the animal body. Its inability to do this may be due to the fact that it cannot digest and therefore cannot feed upon the proteins of the body or it may result from the fact that the ferments of the body-cell do digest and destroy the bacterial proteins. Herein lies the explanation of all forms of bacterial immunity either natural or acquired. Toxin immunity is quite a different thing and will not be treated in this paper.

In case of exposure, the chance of infection depends upon several variables, such as the number and viability of the organisms introduced and the state of health or capability of resistance on the part of the animal. In man the effectiveness of the defensive ferments is influenced by heredity, age, food and possibly other conditions. The great fatality of measles and tuberculosis among those peoples who have inherited no resistance to these diseases is well known. That infants and adults are physiologically protected to a marked degree against diphtheria while children are largely without protection has been demonstrated by Shick (Münch. med. Wochenschrift,

Digitized by Google

1913, p. 2608) and others. We have long known that typhus, plague, beriberi, scurvy and pellagra are most in evidence when abundance and variety in food are lacking, and the work of Osborne and Mendel (Jour. biolog. Chem., 1913, xv, 311), McCollum and Davis (ibid., xiv, 40), Wellman and Bass (Jour. Trop. Med., 1913), Funk (Münch. med. Wochenschrift, 1913, p. 2614) and others on the vitamines promises much.

When the infecting organism multiplies rapidly and soon leads to general sensitization of the body-cells, the disease developed is acute. On the other hand, when the invading organism finds the conditions for its growth less favorable, it multiplies slowly and only imperfectly and locally sensitizes the body-cells, the disease is chronic. When the virus is widely distributed throughout the body and sensitization is also general, the disease is systemic. On the other hand, when the virus and sensitization are restricted the disease is local. In cattle and sheep the anthrax bacillus grows rapidly, becomes abundant in the blood, sensitizes generally and consequently develops an acute systemic disease. On the other hand, in the hog the growth of the anthrax bacillus is restricted to the lymphatic glands, sensitization is equally local, and the disease is both local and chronic.

That a given pathogenic bacterium may grow in one animal and not in a closely related species is illustrated by the susceptibility of the ordinary sheep and the immunity of the Algerian variety to anthrax. Koch found that the bacilli of mouse septicæmia and the cocci that induce necrosis multiply simultaneously in the white mouse, but when field mice are inoculated with mixed cultures the latter infects while the former fails to develop. Even natural immunity is only relative and may be overcome (1) by massive doses of the virus as was demonstrated by Chaveau for Algerian sheep, (2) by lowering the temperature, as shown by Pasteur for chickens, (3) by starvation, as exemplified by Canalis and Morpurgo for pigeons—all with anthrax.

One very important thing that we have learned in recent years is that the ferments produced by the body-cells may be

Digitized by Google

and are modified under certain conditions. The cell may form a wholly new ferment, or one whose activity is so modified that it may be so regarded. It is either a new ferment or the old one greatly modified and intensified in its action. We have utilized this function of the body-cells for more than a hundred years in vaccination against smallpox, but this use has been wholly empirical until recently, when it was scientifically explained by the researches of von Pirquet. Smallpox virus is pathogenic to the man who has not suffered an attack of the disease or has not been vaccinated, while to the man who has recovered from the disease and to the one who has been properly vaccinated it is not pathogenic. By the introduction of the vaccine organism, which is a non-virulent form of the virus, the body-cells are trained, as it were, to digest and destroy its proteins, and this leads to the immediate destruction of the virus on subsequent exposure to the disease. The same principle holds in typhoid vaccination with the dead bacillus now so widely and successfully practised.

My students and I have convinced ourselves, at least, of the following: (*a*) The infective bacteria, taking the colon, typhoid, tubercle and the pneumococcus as types, contain an intracellular poison. (*b*) This is not a toxin because it is not destroyed by heat; it is not specific, it produces no antibody when injected into animals in increasing non-fatal doses. (*c*) These bacteria elaborate no soluble toxin or poison. In old cultures there may be a trace of poison but this results from the autolysis of the cells and is not a cellular secretion. (*d*) This poison can be obtained in soluble form only after cleavage of the cellular proteins, which may be accomplished by superheated steam, dilute acids or alkalies. (*e*) This poison is a group in the protein molecule. (*f*) It exists in all true proteins, in pathogenic and non-pathogenic bacteria and in vegetable and animal proteins. (*g*) It is a split product of the protein molecule. (*h*) It may result from the cleavage action of proteolytic ferments. (*i*) In most vegetable and animal proteins the poisonous group is neutralized by combination with non-poisonous groups; consequently such proteins have no poisonous action until they

Digitized by Google

undergo molecular disruption. (*j*) The poisonous group is common to all proteins; it is probably not chemically identical in different proteins, but is so nearly so that its gross toxicological action is the same. We designate it as the central or primary group in the protein molecule. (*k*) This primary group is poisonous because of the avidity with which it combines with secondary groups in the proteins of the animal body. (*l*) The specificity of proteins lies in their secondary, non-poisonous groups. It is in these that one protein chemically and biologically differs from another. (*m*) Biological relationship among proteins is determined by the chemical structure of their molecules. There are as many kinds of proteins as there are kinds of cells. (*n*) The specificity of the infective bacteria does not lie in the poisonous group of their proteins, for this has the same action in all, but in the non-poisonous groups. (*o*) The poison that kills in all the infectious diseases is the same. (*p*) The symptoms of the infections differ on account of the organ or tissue in which the virus accumulates and where it is split up and its poison liberated. (*q*) The ferment which causes the cleavage of the bacterial proteins in the different infectious diseases is specific. How strictly this is true can be determined only by more exhaustive and exact study.

When a fatal dose of a living virulent culture of the colon bacillus is injected into the peritoneal cavity of a guinea pig the following effects result: For a period of time which usually varies from eight to twelve hours the animal remains apparently normal. Its temperature may fluctuate slightly but not beyond the normal limits. The coat is not roughened and the position and behavior of the animal in no way distinguish it from its untreated fellows. This is the period of incubation and varies within certain time limits, but within these it is fairly constant. During this time the bacilli are multiplying enormously in the animal body. They are converting animal proteins into bacterial proteins. This is largely a synthetic or constructive process. The relatively simple, soluble proteins of the animal body with but little change are woven into the more complex structure of the bacterial proteins. The soluble

Digitized by Google

proteins of blood and lymph are built into the cellular proteins of the bacteria. There is no liberation of the protein poison and consequently no disturbance in the well-being of the host. It seems plain from this that the multiplication of bacteria in the animal body is not the direct and immediate cause of the symptoms of disease. When multiplication is most rapid and unobstructed there are no symptoms and in fact disease is not in evidence. During the period of incubation of an infectious disease the invading organism supplies the ferment; the soluble proteins of the animal body constitute the substrate; the process is constructive; simple proteins are built into more complex ones; no protein poison is liberated, and no recognizable symptoms mark the progress of the infection. Still, in the development of the phenomena of infection the period of incubation is critical, and the rate at which the infecting virus multiplies during this time is an important factor in determining the final outcome. The more virulent the virus, the more rapidly does it multiply and this means a larger amount of animal protein converted into bacterial protein. Rosenthal (Archiv. f. Hygiene, 1913, lxxxi, 81) has shown by means of his bacteriometer that the more virulent a bacterium the more rapidly does it multiply.

Somewhat abruptly there is a change in the behavior of our inoculated guinea pig. The hairs behind the ears begin to stand out and soon the entire coat becomes rough. It no longer eats, but retires to one corner of the cage and seems to be in distress. Slight pressure over the abdomen elicits evidence of pain and the temperature begins to fall and continues to do so until death. In case of recovery a rise in temperature is the first evidence of improvement. The characteristic lesion is a marked hemorrhagic peritonitis.

This somewhat abrupt change in the condition of the animal marks the end of the period of incubation and the beginning of the active disease. The animal cells have become sensitized and are now pouring out a specific ferment which digests the bacterial proteins. In the active stage of the disease, the animal cells supply the ferment; the bacterial proteins constitute

Digitized by Google

the substrate; complex cellular proteins are split into simpler bodies; the process is analytic and destructive; the protein poison is liberated; the symptoms of disease develop, and life is placed in jeopardy.

It must not be understood that the processes that characterize the period of incubation and those that develop the active stage of the disease are separated by a well-marked time limit and that the former wholly cease before the latter begin. This is not my understanding at all. Growth may be extending in one part of an organ, such as the lungs in pneumonia, while the destructive process predominates in another part. Only those cells with which the bacterial protein comes in contact are sensitized, and sensitization may be quite localized.

We take a second guinea pig and inject into its peritoneal cavity a fatal quantity of the dead cellular substance of the colon bacillus. In this experiment we cut ont one of the factors in the development of an infection, the growth of the bacillus in the animal body. This has been done *in vitro* and we inject into the peritoneal cavity enough of the cellular poison to kill. When this is done the animal remains quite well for about four hours, after which it shows symptoms identical with those manifested by its fellow which had been inoculated with the living culture. The lesions induced in both animals are the same. We conclude from this experiment that a period of about four hours is required to sensitize the cells of the guinea pig sufficiently to enable them to begin the cleavage of the bacterial protein and carry this process to the production of enough poison to so disturb the health of the animal that the effects come within the range of clinical observation. There are involved in the process of the incubation of an infectious disease two important functions. One is the growth of the invading organism and the other is the sensitization of the body-cells. The more rapid the growth of the virus and the greater the amount of foreign protein accumulated at the time when sensitization becomes effective the more disastrous are the results. Fortunately particulate proteins, like bacteria and protozoa, are not so effective in the production of sensitization as are the

Digitized by Google

simple, soluble proteins, such as those of blood-serum. Cell penetration is probably essential to the most perfect sensitization. Equally fortunate is it that the living cellular proteins are not so suddenly disrupted by the ferments produced by the body-cells as are the simple, soluble proteins.

To a third guinea pig we administer a fatal dose of the free protein poison split off from some protein molecule by either chemical agents or by a ferment acting *in vitro*. In this instance we cut out the whole period of incubation and the animal dies as quickly as it would from a dose of hydrocyanic acid. The infective agent has been grown artificially, the cleavage has been effected *in vitro* and the ready formed poison acts with the promptness that characterizes the action of other deadly chemical poisons. These experiments have been repeated in my laboratory many times with varied proteins, living and dead, particulate and in solution, of bacterial, vegetable and animal origin, and with their split products. If I have correctly interpreted them they throw much light on the phenomena of infection. However, before we question the correctness of the interpretation we must proceed with our experimentation.

The older literature shows that a few observers have long known that the parenteral introduction of diverse proteins is followed by the development of fever. There is an article by Gamaleia (Annales de l'Institut Pasteur, 1888, ii, 229), written twenty-five years ago, to which I wish to call attention. The title of the article is interesting: "The Destruction of Microbes in the Febrile Organism." Gamaleia showed that fever followed the parenteral introduction of dead as well as living bacteria, either pathogenic or non-pathogenic. He concluded from these experiments that fever is not a phenomenon of bacterial growth in the body. He found that the less virulent the infecting organism the higher and the more persistent is the fever. A rabbit inoculated with the anthrax bacillus runs a fever for only a few hours, when the temperature falls and death results; while one inoculated with the second vaccine runs a fever of three days. When a rabbit is inoculated with a

Digitized by Google

highly virulent anthrax bacillus, it may show but little or no elevation of temperature and dies within from five to seven hours. Gamaleia made similar experimental observations on other diseases and came to the following conclusion: The febrile process is not a result of the action of the bacteria, but on the contrary, is due to a reaction of the organism against their presence and results in their destruction. I feel that I am fully justified in offering these experiments, made a quarter of a century ago, as supporting my theory or explanation of the phenomena of infection.

In 1909 (Jour. Am. Med. Assn., Aug. 23) it was shown by work in my laboratory that fever could be induced experimentally in animals by the parenteral administration of proteins of diverse origin and structure, and that by modifying the size and frequency of the dose, the type of the fever could be determined at will. We produced an acute fever, the temperature rising to 107° and terminating fatally in a few hours, remittent and intermittent and continued fevers. The last mentioned furnished charts in no way distinguishable from those of typhoid fever. Not only can fever be induced but its accompaniments also. In continued fever thus produced there is increased nitrogen elimination, emaciation, loss of appetite, and lassitude and decreased urinary secretion. These experiments were amplified (Zeitschrift f. Immunitatsforschung, ix, 458) and have been confirmed by Friedberger and others. Protein fever, which includes practically all clinical fevers, is a result of parenteral protein digestion. In this process the animal cells supply the ferment and the foreign protein serves as substrate. The foreign protein may be living or dead, formed or without form. It may be detached or dead tissue from the animal's own body, as after burns. It may be absorbed from some mucous surface, as in hay fever. It may be artifically introduced, as in serum disease. It is usually a living protein, as in the infectious diseases.

There are two kinds of parenteral proteolytic ferments, nonspecific and specific. The former are normally present in the blood and tissues, especially in the first. They differ in kind

Digitized by Google

in different species and in amount and efficiency in different individuals. Their function is to digest and dispose of foreign proteins that find their way into the blood and tissues. Within limits they are general proteolytic ferments, as are those of the alimentary canal, but the variety of proteins upon which they act is more limited. They constitute the most important factor in racial and individual immunity. We are immune to most bacteria and protozoa, not because they do not elaborate poisons, for every protein molecule contains its poisonous group, but because they are destroyed by the general proteolytic enzymes as soon as they enter the body and are not allowed to multiply. These non-specific parenteral ferments are probably secretions of certain specialized cells, as the leucocytes. Under normal conditions these enzymes are capable of digesting those proteins upon which they act only in small amounts; but the cells which elaborate them may be stimulated in their activity. Whether or not these enzymes become specific when brought into contact with certain proteins has not been determined. The immunity secured by these enzymes is limited in extent and transitory in duration.

The specific, parenteral, proteolytic enzymes are not normal products of the body-cells, but are brought into existence under the stimulation of those proteins, introduced into the blood and tissues, which on account of their nature or amount escape the action of the non-specific ferments. A protein introduced into the blood and not promptly and fully digested by the non-specific enzymes is discharged from the blood current and deposited in some tissue, the cells of which after a time develop a specific ferment which splits up this protein while it is not capable of digesting any other. For certain proteins there are certain predilection organs and tissues in which they are stored, either exclusively or most abundantly: the pneumococcus in the lungs; the typhoid bacillus in the spleen, mesenteric and other glands; the viruses of the exanthematous diseases in the skin, etc.

For the development of the specific proteolytic ferments time is required and this varies with the sensitizing protein and

Digitized by Google

probably with the tissue in which it is deposited. The development of these ferments necessitates changes in the chemical constitution of the protein molecules of the body-cells and in this way the body-cells acquire a new function, which subsequently is brought into operation only by that protein to which its existence is due. As a result of this rearrangement in molecular structure the cell stores up a specific zymogen which is activated by contact with its specific protein.

Whether the products of digestion with the non-specific ferments and those elaborated by the specific enzymes are identical or not remains to be ascertained. The presence of a poisonous group in the protein molecules is disclosed in both enteral and parenteral digestion as well as by cleavage with chemical agents or enzymes *in vitro*. In enteral digestion the poison is most apparent in the peptone molecule, which is large, complex and non-diffusible. Further action of the alimentary enzymes splits the peptone into harmless amino-acids. The cleavage of proteins by chemical agents is a crude process, in which much of the poison is destroyed. When the poison is formed in the alimentary canal the animal is protected from its injurious effects by the walls and by its ultimate destruction. When the poison is liberated parenterally there are no protecting walls.

There are certainly other causes of fever, but the fever of the infectious diseases results from the parenteral digestion of the infecting agent by specific secretions elaborated by the body-cells; it is a phenomenon of the disposal of foreign and harmful material and it must be regarded as beneficent. However, there is a point above which it becomes a danger *per se*. In parenteral digestion the following sources of heat production must be evident: (1) The unaccustomed stimulation and consequent increased activity of the cells which supply the enzyme must be the source of no inconsiderable increase in heat production. (2) The cleavage of the foreign protein increases the liberation of heat. (3) The reaction between the product of the digestion and the tissues must lead to increased heat production. I regard the first and last of these as the more important sources of the over-production of heat in an infectious

Digitized by Google

disease. When the poison is liberated rapidly and abundantly the temperature falls and death is imminent.

There are many conditions which affect the course of a fever and some of these may be mentioned. Some viruses sensitize more quickly and thoroughly than others. It is probable that the living cells, so long as they are living, do not sensitize. Some of the virus protein must go into solution before cell penetration, which seems essential to thorough sensitization, can occur. A living colon bacillus of not more than twenty-four hours' growth, when injected intraperitoneally in a guinea pig, requires about ten hours to sensitize. With the dead bacillus the time is reduced to half, while with old autolysed cultures in which the sensitizing group is already in solution the time is still further shortened. Some pathogenic organisms, like the tubercle bacillus, have been so long parasitic that they have learned to protect themselves by deposits of fats and waxes. In this way they are probably protected to some extent against the destructive ferments elaborated by the body-cells. In all acute infections the destruction of the invading organism is modified and delayed by the altered relation between substrate and ferment and the accumulation of fermentative products. All these questions are but little understood and their solution must await further research.

I have given the new theory of the phenomena of infection as I understand it. The attack on these problems has only commenced and I do not hold that my opinions possess in every particular the force of demonstrated facts. If they prove to be provocative of further and more exact research I shall feel that they have been justified.

I shall now take up some of the facts for and against this theory and try to make impartial statements concerning them. In the first place it is true, as Doerr states, that it has not been conclusively demonstrated that the poison formed *in vitro* is identical with that elaborated *in vivo*. In fact we do not know the exact nature of the poison produced by the disruption of the protein molecule by chemical agents. I hold that this poison is a group in the protein molecule. Others question this and

Digitized by Google

hold to the endotoxin theory as first elaborated by R. Pfeiffer. So long as the poison was obtained only from complex proteins, such as bacterial cellular substances, the mixed proteins of blood-serum and egg-white which is known to be a protein mixture, my opponents had an argument which I could not meet, but some proteins, such as edestin, are believed by all students of protein chemistry to be chemical units, just as much so as crystallized bodies. We take edestin and split it into poisonous and non-poisonous portions. We inject the former into a fresh guinea pig and it kills the animal promptly after the development of certain definite and well-marked symptoms. We take another fresh guinea pig and sensitize it to edestin and after a proper interval we give the same animal a second injection of edestin. This animal develops the same symptoms in the same time and in the same sequence as the other and the postmortem findings in the two are identical. We know that the edestin injected into the animal contains the protein poison which we may liberate *in vitro*. It seems that the only conclusion justifiable from these facts is that in both instances the animal dies from the same poison and that by the process of sensitization the capability of splitting up the edestin molecules has been developed. Besides, the blood-serum of an animal sensitized to egg-white will, when incubated with egg-white in proper proportion *in vitro,* produce a poison which kills a fresh animal with the same symptoms and with the same postmortem condition as are developed on reinjection in a sensitized animal, while the blood of a fresh animal has no such action on egg-white *in vitro*. From these facts I draw the following conclusions: (1) The protein poison is a group in the protein molecule. (2) In a sensitized animal's blood-serum there is some agent capable of splitting up a protein and thus liberating a poison and that this something does not exist in the blood-serum of the unsensitized animal. If there be a fallacy in this reasoning I cannot see it. If it should be found that edestin and other proteins, believed to be chemical units, are not such, then my first conclusion is not wholly justified.

I do not claim that the protein poison formed *in vitro* by the

Digitized by Google

chemical disruption of the protein molecule is identical with that elaborated *in vivo* by specific ferments, but that they are closely related chemically is inferred from their physiological action. As I have stated, we do not know the chemical structure of the protein poison. We are certain that it is not an amino-acid, although it may be closely related to one of these. In its action the protein poison seems quite similar if not identical with the histamine of Barger and Dale. It will probably be found that the protein molecule contains a whole spectrum of poisons, one differing from another in some slight alteration in structure.

Years ago R. Pfeiffer demonstrated that cholera, typhoid, colon and many other bacilli secrete no toxin, but that the cellular proteins of these organisms are poisonous. In the abdominal cavities of animals previously treated with these bacteria, when new injections are made, the bacterial cells dissolve like sugar or salt in water, but notwithstanding this destruction of the bacteria the animal dies.

Indeed death is due to the destruction of the bacterial cells and the consequent liberation of the protein poison. When the amount of cellular substance is insufficient to furnish a fatal dose of the poison the animal survives and escapes infection. I regard Pfeiffer's phenomenon as the basis of lytic immunity and it must be evident that this form of immunity is not in any way comparable to that induced by toxins. Pfeiffer was certainly wrong in explaining this phenomenon on the supposition that the bacterial cell contains an endotoxin. The harmful contents of the cellular substance is not a toxin, in the sense that this term is now used, but is a poison. The next important work done along this line was that of Weichardt, who found that the blood-serum of rabbits previously treated repeatedly with placental proteins dissolves the same both *in vitro* and *in vivo* with the liberation of a poison. This experiment was a forerunner of Abherhalden's test for pregnancy. Next came the work of Friedemann, who showed that red blood-corpuscles may be dissolved without setting free an active poison, and, on the other hand, the poisonous group of the

Digitized by Google

hæmoglobin molecule may be extracted without dissolving the corpuscles. Thomsen demonstrated that in guinea pigs sensitized with erythrocytes there is no recognizable hæmolysis on reinjection, although anaphylactic shock results. When unbroken corpuscles are employed the anaphylactic poison may come from either the hæmoglobin or the stroma or from both. We have anaphylactized animals with hæmoglobin and with stroma. The former is easily done on account of the ready solubility of the hæmoglobin. The stroma is not so good an anaphylactogen for the opposite reason. Friedberger and Vallardi have found that only by having stroma, amboceptor and complement in proper proportions can the anaphylactic poison be prepared. Neufeld and Dold have found that anaphylactic poison can be prepared from bacteria without cytolysis. In regard to the anaphylatoxin of Friedberger it seems most likely that the matrix of this poison is the serum since it has been prepared by Bordet by incubating serum with agar and by Nathan by employing starch. Still, if it be proven that it comes from the serum, this in no way disturbs the theory that it is the protein poison. Our protein poison comes certainly from the protein molecule. It cannot be a ferment as we understand ferments at present. It is thermo-stabile and it elaborates no antibody and yet it may be identical with anaphylatoxin, for whether the latter comes from bacterial cells or from the serum it is of protein origin.

Loewitt and Barger (Archiv. f. exp. Path. u. Pharm., 1913, lxxiii, 164) have demonstrated that agar contains an anaphylactogenic protein. This does not prove that the poison produced in Bordet's experiments *does* come from the protein in the agar but it shows that this *may* be the source of the poison. The protein in agar undoubtedly has a large surface exposure and this renders it especially susceptible to ferment action. I have twice tried to prepare the protein poison by the cleavage of agar with chemical agents, but without success. However, this does not prove that a proteolytic ferment might not accomplish this purpose, since the chemical method is crude and destructive of a large amount of the poison.

Digitized by Google

Schlecht (Arch. f. exp. Path. u. Pharm., 1912, lxvii, 137) found that on reinjection of a sensitized animal the eosinophiles are increased, and Chancellor (Zeitschrift f. die gesamte exp. Med., 1913, ii, 29) finds that there is also an increase in the same corpuscles on the injection of the protein poison. So far as it goes this indicates that the poison liberated in anaphylactic shock and that formed from proteins by my method are similar in their effects.

The blood of an animal killed by anaphylactic shock coagulates slowly, while that of animals killed with the protein poison prepared by chemical agents coagulates in the usual time. This might be regarded as evidence that the poison formed *in vivo* and that prepared *in vitro* are not identical, but the agent which leads to retardation of coagulation may be one of the non-poisonous groups liberated on the cleavage of the protein molecules in the body. However, the protein poison obtained by chemical means from certain proteins, such as the tubercle bacillus, does prevent the coagulation of the blood. This is the first evidence that I have found of any dissimilarity in the action of the protein poison as obtained from different proteins. It has been shown by Loewitt (Arch. f. exp. Path. u. Pharm., 1912, lxviii, 85) and Waele (Zeitschrift f. Immunitätsforschung, 1913, xvii, 314) that a non-coagulable blood is not always in evidence in anaphylactic shock.

The fundamental fact in the work recently done by Abderhalden, the full import of which we cannot yet determine, rests upon the development of ferments as a result of the parenteral introduction of foreign proteins. How strictly specific these ferments are is a matter which must be measured by larger experience.

Weinland first showed that invertase is developed in dogs by the parenteral introduction of cane-sugar, and this work has been amplified by Abderhalden, Heilner and others until it has been demonstrated that the cells of the animal body can be trained to elaborate specific proteolytic, amylolytic and lipolytic ferments. The presence of specific ferments in the

Digitized by Google

blood-serum is now being used in the diagnosis of pregnancy, cancer and dementia præcox.

If I correctly interpret the recently reported experiments of Thiele and Embleton (Zeitschrift f. Immunitätsforschung, 1913, xix, 643, 666) they furnish strong evidence in favor of the theory which I have formulated. These investigators have developed the following points: (1) When the normal protective ferments of the animal body are inhibited in their activity, bacteria which under normal conditions are non-pathogenic become pathogenic. It is well known that ferment activity may be retarded by hypertonic saline solutions. When such non-pathogenic micro-organisms as *Sarcina lutea* and *B. prodigiosus* and others are suspended in from two to five per cent. salt solution and injected into the abdominal cavity of the guinea pig, the normal lytic ferment of the animal is inhibited; the micro-organism multiples and kills. In other words, a harmless bacterium is converted into a fatal one by holding in abeyance the normal protective function of the body. Years ago Buchner demonstrated that the alexin of blood-serum is highly sensitive to salt content, and by variations in this the activity of the ferment may be hastened, lowered or wholly arrested. In this connection it may be interesting to record the fact that some physicians believe that a heavily salted diet predisposes to pneumonia. (2) The blood and exudates of animals dying of infectious diseases are shown by the application of the ninhydrin and biuret tests to their diffusates to contain protein cleavage bodies, which are not present under normal conditions. These proteoclastic bodies could hardly have their origin elsewhere than in the cleavage of the bacterial proteins. (3) These cleavage bodies found in the blood of animals dying of the infectious diseases develop typical anaphylactic shock in fresh animals when injected intravenously.

The studies of the autolytic cleavage products, obtained from bacterial cellular substances, as reported by Rosenow (Jour. Infec. Dis., ix) and Cole (Jour. Exp. Med., xvi) show conclusively that the bacterial cells contain a poison—not an endotoxin, because no antibody can be produced. It is true that

Digitized by Google

these studies, taken alone, leave it in doubt whether the poison is a group in a larger molecule or constitutes a chemical entity, but surely the poison obtained from edestin and similar pure proteins must exist primarily as a group in a larger molecule. It must be admitted that the great weight of evidence is against the existence of endotoxins in the sense suggested some years ago by R. Pfeiffer.

Edmunds (Zeitschrift f. Immunitätsforschung, 1913, xvii, 105, also unpublished research) has shown that the physiological action of my protein poison in dogs and cats is essentially the same as that manifested in sensitized animals on reinjection and the same has been shown by several observers to be true in guinea pigs. While identity in physiological action does not establish chemical identity, it certainly suggests similarity in chemical structure.

Auer and Van Slyke (Jour. Exp. Med., 1913, xviii, 210), using the highly exact method of the latter for the determination of amino-nitrogen, find that the lungs of guinea pigs killed by anaphylactic shock on intravenous reinjection of from 0.5 to 0.9 c.c. of horse serum do not yield more amino-nitrogen than do the lungs of guinea pigs killed by injecting air into the veins directly after they have received intravenous injections of 0.9 c.c. of horse serum, and they conclude: "This investigation gives no support to the hypothesis that the true anaphylactic lung of the guinea pig is caused by protein split products." I am not inclined to attach much weight to this evidence, for the following reasons: (1) The total amount of protein introduced on reinjection was small; 0.5 c.c. of horse serum contains at the most not more than 40 mg. of total protein. (2) The lungs were weighed only to within 10 mg., *i.e.*, the error may have amounted to this. (3) The protein poison while still impure kills guinea pigs when given intravenously in doses of 0.5 mg. (4) While we do not know just what the protein poison is, we do know that it is not an amino-acid. (5) " In Table II when the free amino-nitrogen not only of the amino-acids but also of the peptones, albumoses, etc., was determined, we find the average after acute anaphylactic death

Digitized by Google

(ten animals) to be 61.8 mg. per 100 grammes of lung tissue, while controls (ten animals) show 58.5 mg. for the same amount of tissue; the small difference between the two averages (3 mg.) is without significance, as it falls within the range of normal variation.'' Three milligrammes of nitrogen represent at the least from fifteen to eighteen fatal doses of the protein poison. When a method for the recovery of a poison from the tissue fails to discover fifteen times the quantity necessary to kill, no great excellence for such a method can be claimed. (6) '' When the non-coagulable amino-nitrogen after hydrolysis with hydrochloric acid was determined in five anaphylactic and five control lungs the results again showed no significant differences; the average yield of the anaphylactic lungs per 100 grammes of tissue was 172.6 mg., while the average for the controls was 171.2 mg.'' Here, there is in each 100 g. of the lungs of the anaphylactized animal enough more nitrogen, than in like tissue of the control, to account for from six to nine fatal doses of the poison. We know but little concerning the nature of the protein split products formed in parenteral digestion, but since they are recognized by the ninhydrin and biuret tests they cannot, wholly at least, consist of amino-acids. It is true that certain simple peptides may be split by parenteral ferments into their component amino-acids.

Acute anaphylactic shock is so striking in its manifestations that it has delayed studies of chronic protein intoxication, in which, I doubt not, there lies a rich and profitable field of research. Every foreign protein finding its way into the blood and tissues is more or less injurious to the body-cells. It may be directly harmful or it may act through its split products. When repeatedly introduced the body-cells become sensitized and split it up. When the intervals between the introductions are short there can be nothing like anaphylactic shock, but parenteral digestion has been established and the protein poison is liberated, possibly not in quantity sufficient to develop recognizable symptoms, but there results a chronic poisoning. If the theory which I have developed be true, the lesions of the infectious diseases are, in part at least, due to protein poisoning.

Digitized by Google

Moreover, the disease needs not be an infectious one in order to lead to either acute or chronic protein poisoning. The absorption of undigested or partially digested proteins from the alimentary canal may be quite as harmful as inoculation with a living virus. It seems to me that we are now quite justified in speaking of the "Albuminal Diseases," including under this title all health disturbances due to the parenteral introduction of foreign proteins, be they living or dead, organized or unorganized. The description given by Richet of his experiments on anaphylaxis in dogs suggests strikingly cholera nostras in man. Schittenhelm and Weichardt induced an "enteritis anaphylactica"; in like manner, Friedberger (Deutsche med. Wochenschrift, 1911, xxxvii, 481) developed pneumonia in sensitized guinea pigs by spraying horse serum into the trachea. This has been confirmed by Ishioka (Deutsche Arch. f. klin. Med., 1912, cvii, 500) and a careful histological study of the lungs in this condition has been made by Schlecht and Schwenker (ibid., cviii, 405). It seems highly probable that we have been wrong in believing that all diseased conditions are due to infections, many of which are secondary. In this connection I wish to call attention to the valuable research reported by Longcope (Jour. Exp. Med., 1913, xviii, 678), who has induced nephritis in rabbits and dogs by repeated injections of horse serum and egg-white. When we consider the care with which nature protects the body-cells from foreign proteins by the radical changes wrought in their structure by alimentary digestion, and since we know that every unbroken protein contains a highly poisonous group, we should proceed cautiously in the employment of serum and vaccine therapy. The value of diphtheria and some other antitoxins has been demonstrated and the good accomplished with these agents constitutes one of the great triumphs of modern medicine, but much of the protein therapy now so largely employed is without scientific justification. I have tried earnestly to so disrupt the protein molecule of certain pathogenic bacteria as to obtain a non-poisonous, sensitizing group which might be of value in either prophylactic or curative treatment, but without practi-

Digitized by Google

cal success. I have obtained from the cellular substances of the colon, typhoid and tubercle bacilli non-poisonous sensitizing proteins. Those from the colon and typhoid give some degree of immunity to subsequent inoculation with respective living cultures, but the protection thus secured is low in degree and ephemeral; while that from the tubercle bacillus fails to protect experimental animals. I must therefore report failure with glimpses of that will-o'-the-wisp which haunts the laboratory of every investigator. When one thinks of the great number of cleavage lines that run through the large protein molecule he must not be surprised when the gem with perfect facets, which he seeks, is not revealed at the first stroke of the hammer.

As has been stated, we have split proteins into poisonous and non-poisonous portions. This has been done with proteins of most diverse origin, bacterial, vegetable and animal, and we have found no true protein which has failed to undergo this cleavage. Certain pseudo-proteins, like gelatin, do not respond to this test, but all true proteins, as far as tested, have been split into poisonous and non-poisonous portions. This is the foundation stone of our theory of protein sensitization. All true proteins are sensitizers, and so far it has not been shown that sensitization can be established by any non-protein substance. All sensitizers develop symptoms of poisoning on reinjection. These symptoms induced by reinjection are identical in manifestation and sequence with those induced in the fresh animal by the injection of the poison split off from the protein molecule by chemical agents, or by the ferments in the serum or organ extracts of sensitized animals. Therefore, we have concluded that anaphylactic shock is due to the cleavage of the molecule of the protein sensitizer on reinjection, and the liberation of the protein poison, and this cleavage is due to a specific proteolytic enzyme developed in the cells of the animal body as a result of the first injection. We have repeatedly shown that the poisonous group obtained from the protein molecule by cleavage with chemicals or with ferments does not sensitize animals. This is contrary to the generally

Digitized by Google

accepted view, and our claim on this point has met with either silence or denial, but we have tested this matter so often and with poisons obtained from so many and such a variety of proteins that we have no hesitancy in affirming that the poisonous group in the protein molecule does not sensitize animals. But it is said that toxins are necessary to elaborate antitoxins, and that the latter can be produced in no other way. This is true, but the protein poisons are not toxins, and they lead to the elaboration of no antibodies. The toxins are specific; the protein poisons are not. The blood-serum of an animal treated properly with a toxin neutralizes the toxin both *in vitro* and *in vivo,* while the blood-serum of a sensitized animal renders the protein with which the animal has been treated, when brought in contact with it under proper conditions, either *in vitro* or *in vivo,* poisonous. It seems to us that it has been positively demonstrated that the sensitizing and toxic groups in the protein molecule are not the same. It might be argued that in ordinary protein mixtures, such as blood-serum and egg-white, one protein may contain the sensitizing group and another the toxic group. This may be true, but when pure proteins, such as edestin, are used the two groups must exist in the same molecule. The specificity of proteins is demonstrated in sensitization. The toxic group shows no specificity. This property characterizes the sensitizing group, and it is in these groups that the fundamental and characteristic property of each protein resides. The exact structure and chemical nature of neither the sensitizing nor the poisonous groups have been determined. The latter seems to be physiologically the same in all proteins, the former is specific in every protein. By our method, the poisonous group is easily obtained; not in a chemically pure condition, but so that its presence can be demonstrated. The poisonous group, being the same in all proteins, is obtained from all by the same or by like methods. The sensitizing group, being the same in no two proteins, cannot be isolated from all by the same method. We have been able to obtain specific sensitizing groups from colon, typhoid and tubercle protein quite uniformly. From the pneumococcus

Digitized by Google

and related organisms we have never succeeded in obtaining a sensitizing group. From egg-white we have rarely succeeded, generally failed. It seems evident to us that the sensitizing groups in many proteins are highly labile bodies, probably of such delicate structure that they easily fall to pieces.

If sensitizers are ever to have a legitimate place in the treatment of disease, it will be of the highest importance to obtain them free from the poisonous group. Every time an unbroken protein is introduced into the body it carries with it, and as a part of it, a poison. From the very careless, rash and unwarranted way in which " vaccines " of most diverse origin and composition are now used in the treatment of disease, this matter certainly cannot be understood or its danger appreciated by those who subject their patients to such risks. It should be clearly understood that all proteins contain a poisonous group—a substance which in a dose of 0.5 mg. injected intravenously kills a guinea pig. This poison is present in all the so-called " vaccines " now so largely used, and it is not strange that death occasionally follows the use of " phylacogen " or similar preparations. Not only do these proteins contain a poison, but when introduced parenterally the poison is set free, not in the stomach, from which it may be removed, but in the blood and tissues. It is possible that vaccine therapy may become of great service in the treatment of disease. Even now there are occasional brilliant results which are reported while the failures and disasters are not so widely advertised. But before sensitization can be of great service in a therapeutical way we must secure sensitizers free from poisonous constituents. Until recently the existence of, or the possibility of preparing non-toxic sensitizers has been made evident only by our work. Recently, confirmations of our studies along this line have come: (1) From White and Avery (Jour. Med. Research, 1912, xxvi, 317), who have prepared by our method a sensitizing group from tubercle cell substance. (2) From Zunz (Zeitschrift f. Immunitätsforschung, 1913, xvi, 580), who, as the result of a most exhaustive research, has shown that one

Digitized by Google

of the primary albumoses (the synalbumose of Pick) sensitizes, but does not induce anaphylactic shock on reinjection. Zunz states: Both active and passive anaphylaxis can be induced by the three so-called primary proteoses (hetero-, proto-, and synalbumose), but not by thioalbumose, nor the other so-called secondary proteoses, nor by Siegfried's pepsin-fibrin-peptone-β, nor by any of the abiuret products of peptic, tryptic, or ereptic digestion.

Animals sensitized with hetero-, proto-, or synalbumose develop anaphylactic shock on reinjection with the original serum, acid albumin, hetero- or proto-albumose, but *not* after reinjection with synalbumose, thio-albumose, the other secondary proteoses, pepsin-fibrin-peptone-β, or any of the abiuret products of peptic, tryptic, or ereptic digestion. The hetero- and proto-albumoses both sensitize and induce anaphylactic shock, while synalbumose sensitizes only. It follows, therefore, that sensitization and the production of anaphylactic shock are due to different groups in the protein molecule.

Wells and Osborne (Jour. Infect. Dis., 1913, xii, 341), working with the purest vegetable proteins known, hordein from barley, glutinin from wheat, and gliadin from both wheat and rye, find that:

Guinea pigs sensitized with gliadin from wheat or rye give strong anaphylactic reactions with hordein from barley, but these are not so strong as the reactions obtained with the homologous protein. Similar results are obtained if the sensitizing protein is hordein, and the second injection is gliadin. We have here a common anaphylaxis reaction developed by two chemically distinct but similar proteins of different biological origin, thus indicating that the specificity of the reaction is determined by the chemical constitution of the protein rather than by its biological origin. This is in harmony with the fact that chemically closely related proteins have, as yet, been found only in tissues biologically nearly related.

From the results of these experiments it seems probable that the entire protein molecule is not involved in the specific character of the anaphylaxis reaction, but this is developed by certain groups contained therein, and that one and the same protein molecule may contain two or more such groups.

Digitized by Google

Evidently the view that the protein molecule contains a sensitizing group, one or more, is finding strong experimental support. In our opinion this view was demonstrated by Vaughan and Wheeler (Jour. Infect. Dis., iv, 476) as early as 1907, but recent work, such as that by Zunz, Gay, Wells and Osborne, and others, strengthens the evidence then offered. According to our theory, every protein molecule contains a chemical nucleus, keystone or archon. This is the protein poison, and is physiologically much the same in all proteins. One protein differs from another in its secondary or tertiary groups. In these resides the biological specificity of proteins. Biologically related proteins contain chemically related groups, and in these are found the sensitizing agents. The chemical structure of the protein molecule determines its biological differentiation and development. It is not, therefore, surprising to find that a pure protein from wheat sensitizes to another closely related protein from such a biologically closely related grain as rye. This, however, does not indicate that the proteins from the two grains are wholly identical in chemical structure. It only shows that the two protein molecules contain among their secondary groups identical or closely related atomic combinations. The same can be said of the fact that certain non-pathogenic acid-fast bacteria may, at least partially, sensitize animals to the tubercle bacilus. Biological relationship is determined by the chemical structure of the protein molecule. We hold this to be true of all specific biological tests for proteins, whether they be agglutination, precipitin, lytic, complement deviation, or anaphylactic tests. The chemical structure of the protein molecule determines all these. The form and function of every cell is determined by the chemical structure of its constituent proteins. That the sensitizing agent in the protein molecule resides in its secondary groups is shown by: (*a*) the fact that sensitization is within limits specific; (*b*) the fact that the residues left after stripping off these secondary groups by proteolytic digestion or by the action of dilute bases and acids, do not sensitize. Peptones, polypeptides, amino-acids, and

Digitized by Google

the protein poison do not sensitize to either themselves or to the unbroken proteins from which they have been derived.

We regard the work of Jobling and Bull (Jour. Exp. Med., 1913, xvii, 453) as confirmatory of our studies in every particular. These investigators have studied the action of the cellular substance of the typhoid bacillus and its split products, produced by the action of a proteolytic ferment obtained from leucocytes, and state their findings as follows:

Freshly washed, unheated typhoid bacilli intravenously injected into dogs cause the development of definite symptoms as early as twenty minutes after the injection. Boiling for ten minutes does not destroy the toxic effects of a freshly washed bacterial emulsion. Complete solution of the bacteria (in dilute alkali) of a fresh emulsion does not prevent the removal of the toxic substance with the coagulable proteins. The action of leucoprotease splits the toxic substance to a non-coagulable state, the digested mixtures being toxic after removing the coagulable portion. The mere presence of the leucocytic ferment is not responsible for the toxicity of the filtrate from the digested mixture, and continued digestion destroys the toxicity of a previous toxic mixture. From these observations it is concluded that the toxic properties of freshly washed typhoid bacteria are not entirely due to preformed secretory toxic bodies that are stored in the bacterial bodies, but that these properties are due largely to products formed by hydration of the bacterial proteins through the agency of ferments present in the circulation of the animal previous to the injection, or which become mobile subsequent to the entrance of the foreign bodies into the blood-stream. Since leucocytic ferments can attack the bacterial proteins *in vitro*, it is possible that the leucocytes are a source of the ferments which are active in experimental and natural cases of intoxication with the whole bacteria.

The studies of Pick and Obermeyer (Wiener klin. Wochenschrift, 1904, 1906 and 1912), confirmed and amplified by Landsteimer and Prasek (Zeitschrift f. Immunitätsforschung, 1913, xx, 211), render it highly probable that the specificity of the protein molecule is closely connected with its aromatic group. Furthermore, it is worthy of note that gelatin, in which the aromatic group is wanting, is not a sensitizer. The above-mentioned investigators have shown that when certain substitutions are made in the aromatic group of a protein it loses its specificity. It is also noteworthy that gelatin does not yield

Digitized by Google

the protein poison when disrupted by our chemical method. It seems, therefore, that gelatin contains neither the sensitizing nor the poisonous group.

I must protest against classifying the toxins and anaphylactogens together under the name of "antigen." This term should be reserved for the former. The anaphylactogens produce no antibody. Pick (Kolle and Wassermann Handbuch, zweite Auflage, i, 698) very properly states that diphtheria toxin elaborates neither a precipitin, agglutinin, nor hæmolysin and that it is not an anaphylactogen. He proposes that the toxins be designated as monovalent antigens in contradistinction to the polyvalent antigens which elaborate numerous immune bodies. I can see no reason for calling the anaphylactogens antigens. The anaphylactogens are colloids of highly complex molecular structure, while the latest research all points to the non-protein character of the toxin. As Pick states: Faust finds the active principle of cobra and crotalus venom to be a nitrogen-free sapotoxin; Abel and Ford report that the hæmotoxin of *Amanita phalloides* is a glucoside containing nitrogen and sulphur; Bang and Forssmann state that the hæmolytic component of the red corpuscle is a lipoid; Jacoby claims to have obtained a nitrogen-free ricin; and according to Burckhardt the hæmolysin of *Bacterium putidum* is non-protein. Likewise, tuberculin is an anaphylactogen or not according to the preparation. When free from other constituents of tuberculo-protein it is neither anaphylactogen nor toxin, but a poison. Tuberculo-protein contains an anaphylactogen group but this does not constitute the active principle of tuberculin, which is of relatively simple structure.

Many investigators have failed to sensitize animals with tuberculin, while most have succeeded with dead bacilli and with aqueous extracts. This is not surprising; indeed it is what should have been expected. Tuberculin consists of digested, denatured proteins of relatively simple composition. It is well known that peptones and polypeptides do not sensitize. The protein poison when detached from other groups in the protein molecule sensitizes neither to itself nor to the un-

Digitized by Google

broken protein. The fact that tuberculin does not sensitize or does so imperfectly raises a serious question as to its employment as a therapeutic agent. It is undoubtedly an excellent diagnostic agent because its relatively simple structure may favor its prompt cleavage when injected into an animal already sensitized by the disease. But if it is not a sensitizer its therapeutic good effect, if it has any such effect, must be confined to the possible establishment of a tolerance to the tuberculo-poison. Sensitization to tuberculo-protein can be induced by bacillary emulsions, with watery extracts, and with the non-poisonous residue. If the sensitization secured by the last-mentioned agent is as good as that produced by the others, it has the advantage of not containing any poison. On the other hand, if the therapeutic effect desired consists in the development of a tolerance to the poison, tuberculin must be preferred unless we should use the more completely isolated poison.

There is one statement in the criticism of Doerr, quoted in the beginning of this lecture, to which I have not as yet referred, and which is of great interest. This is the well-established fact that during an attack of measles the person cannot be sensitized to tuberculin. I shall not attempt to explain this phenomenon, but I wish to emphasize its importance. If the theory which I have attempted to develop be true, we have more or less immunity, inherited or acquired, to tuberculosis. This is due to the fact that the cells of our bodies supply ferments more or less destructive to the *Bacillus tuberculosis*. Through inheritance or through previous exposure to this infection, this slight immunity or increased resistance has been developed. In measles it disappears or at least is held in abeyance. Why, we do not know, but it is interesting to call to mind how many cases of tuberculosis begin to develop in an attack of measles. The ubiquitous *B. tuberculosis* strikes when the shield is down.

Digitized by Google

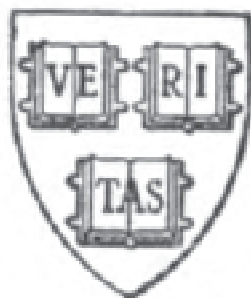
Harvard University

Library of

The Medical School

and

The School of Public Health



The Gift of

3 2044 103 063 491

Digitized by Google