THE TUBERCLE BACILLUS

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IN THE PULMONARY LESION OF MAN

Histobacteriology and its Bearing on the Therapy of Pulmonary Tuberculosis

By GEORGES CANETTI, M.D.
Director of Laboratory, Pasteur Institute, Paris

Foreword by RENE J. DUBOS
and WALSH McDERMOTT

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dans la lésion tuberculeuse du poumon

The translation from the French and the English editing of this monograph represent a joint effort by the following editorial group:

René J. Dubos
H. Joel Gribetz
James Hirsch
Lawrence B. Hobson
Charles LeMaistre
Walsh McDermott
Ralph Tompsett

From the Rockefeller Institute for Medical Research and The New York Hospital-Cornell Medical Center, New York, N.Y.

FOREWORD

With the discovery of the tubercle bacillus and of tuberculin allergy, it appeared as if the high road had been reached toward a complete understanding of the genesis and course of the various types of tuberculous lesions. Unfortunately, the paths followed by the histopathologists and bacteriologists began to part shortly after these discoveries were made; the tissue changes in infection became the preoccupation of the first group of investigators, the characteristics of the etiologic agent the province of the other group. As a result, the student of tuberculous disease is usually confronted with painstakingly detailed studies of either the tissue or the parasite, but he has to rely principally on his own imagination to relate the isolated facts concerning the two aspects of the infectious process. It is precisely the integration of histologic and bacteriologic knowledge which constitutes the central theme of Doctor Canetti's book.

Dr. Canetti's approach to the study of pathogenesis is refreshingly simple. Using quantitative technics (to the extent they are available in this poorly developed field), he made three independent kinds of observation on a large variety of tuberculous lesions from humans: a) histopathologic characteristics of the lesion, b) number of acid-fast bacilli visible in it by microscopy, c) number of bacilli capable of multiplying on egg media. This integration of pathologic and bacteriologic findings permits an objective and comprehensive analysis of the relation of the type of lesion to the multiplication and survival of the bacilli. Dr. Canetti pursues this analysis in the light of the results obtained by animal experimentation, but always on the basis of factual observations on human pathologic material. As he points out, tubercle bacilli exhibit in a very general way the same type of pathogenic behavior in all animal species. There exist, however, anatomic, physiologic and immunologic characteristics peculiar to man which limit the value of generalizations from the results obtained in experimental animals.

The first edition of Dr. Canetti's book appeared in French in 1946, before antimicrobial drugs had come to be generally used in the treatment of tuberculosis. Yet one finds in the 1946 printing a remarkable anticipation of what to expect of antimicrobial therapy, and of its probable failures in certain types of the natural disease. The general discussion also deals with some problems which have recently become of crucial importance—to wit the spontaneous disappearance of bacilli from closed necrotic lesions, or their presence in a form still detectable by microscopy but of reduced ability to grow in vitro or in vivo. Needless to say, these prophetic views are discussed at greater length in the present revised edition.

In addition to its practical importance, this study of the pathogenesis of tuberculosis has great theoretical interest because the disease exemplifies all the complex and subtle phenomena of host-parasite relationships. Dr. Canetti has used logical deductive reasoning to derive from his findings broad philosophic concepts of infection and disease. His book constitutes not only a rich store of valuable documents, but also an intellectual treat for those eager to integrate the practical problems of medicine within the framework of biological philosophy.

René J. Dubos
Walsh McDermott

PREFACE TO THE AMERICAN REVISED EDITION

The histobacteriologic work presented in this book was done between 1940 and 1944, and it was originally written in these years. The French edition came out in 1946, and a Spanish edition in 1948. Three years ago, Dr. Dubos and Dr. McDermott suggested to the author the idea of bringing the book up to date for an English-language edition. The author gave a large amount of time to this revision; the whole therapeutic part of the book has been rewritten. Yet, he looks with some concern on the publication of the new edition today. In scientific work, there are facts but there is also an atmosphere. The facts, if properly observed, will remain but they may take on a strange hue when the atmosphere around them changes.

As is obvious to everybody working in the tuberculosis field, the atmosphere here has never before changed so much in so short a time as it has during the past ten years. The repercussions of this change extend even to the choice of sources from which we draw our knowledge of the disease. Today, the pathology of tuberculosis is studied in lungs removed by surgery rather than in lungs from fatal cases. As a result, certain lesions are discussed extensively in this book, e.g. exudative tuberculous alveolitis and perifocal inflammation, which may seem insignificant in surgical samples deriving from less serious cases and cases that have undergone specific treatment. The material discussed in the book may appear, in part at least, unusual and even depressing.

There is however a positive side to this change in atmosphere. The therapeutic revolution in tuberculosis should make the book more useful than it could possibly be ten years ago. The histologic and bacteriologic effects of antituberculous drugs must be correctly assessed. This, however, cannot be done without knowledge of what the histobacteriology of tuberculosis is in the absence of specific treatment—of what tuberculosis does and does not produce *spontaneously.*

In every experimental study, there is a control group. In that sense, the book brings to the histobacteriologic study of pulmonary tuberculosis, as treated by drugs, the control group which it lacked up to now.

The author is deeply grateful to Dr. Dubos and Dr. McDermott. The idea of this new edition originated with them, they followed its progress closely and removed many obstacles. Such proof of selfless interest and scientific solidarity is very rare indeed. The author also wishes to express his thanks to their colleagues who assisted in the preparation of the edition.

Pasteur Institute, Paris
January, 1955

GEORGES CANETTI

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INTRODUCTION

The reader will find in this volume a systematic study of the fate and properties of tubercle bacilli in pulmonary tuberculous lesions of man. Such a study was necessary for it is not yet known precisely where in the host the bacilli are or are not found, in what type of lesions they are destroyed, where they multiply, and whether the extreme polymorphism of tuberculous lesions corresponds with differences in their bacillary content. Although the author is aware of the many extensive histologic investigations already on record, and of the subsequent flowering of theory and dogma, he believes that fruitful observations can still be made by studying the bacillus at its *pied d'oeuvre* within the lesions that it causes in man.

Not that there has been a lack of bacteriologic study of tuberculous lesions. The bacilli have been stained in inoculation chancres, in miliary tubercles, in nodules, in infiltrates, and in cavities. Their abundance in exudative lesions and their paucity in productive lesions, the characteristic bacillary lining of cavities, as well as the nonbacillary nature of perifocal inflammation, have all been recognized. It is unlikely that many important facts remain to be discovered in this domain. But no attempt has been made to assemble the isolated observations made in the various types of foci, to follow the bacilli in all types of lesions and thus substitute for the fragmentary view, one which would extract from individual facts their full potential significance. There has been little attempt to use the properties and behavior of the bacillus as basis for the elaboration of a theory of pathogenesis. The extensive microscopic studies of the lesion are purely histogenetic in nature, and in them the bacillus is barely considered. Yet, to write of the development of a lesion without regard to its etiologic agent is comparable to writing the history of a war without mentioning one of the adversaries!

One can obtain from such studies a chronologic knowledge of the facts without an explanation of them. As understanding is the ultimate goal, one is inclined to theorize about the unknown. Obscure actions and

mechanisms, imaginary forces and improbable influences often are invoked. Thus the inevitable hypothetic element is increased many-fold. Hence the weakness of purely histogenetic studies, even those chronologically exact. It is necessary to substitute for them a histobacteriogenesis; that is precisely the object of the present work.

A moment's reflection in regard to current notions will demonstrate the necessity of the histobacteriologic point of view. Let us consider allergy. It is, in the most general meaning of the word, a change in the mode of reaction of the organism to a given aggression—in our case that caused by the tubercle bacillus. The histologic manifestation of this allergy, namely appearance within the lesion of new modes of reaction, is one of the key problems of tuberculosis. It has haunted the minds of investigators for several decades. But on what ground is one justified in attributing a lesion to allergy, that is, to an altered reactivity of the organism? To the fact that the lesion differs in type from another? Thus exudative lesions are often considered as allergic in contrast to productive reactions, but the inverse relationship has also been proposed. In reality simple bacteriologic differences of quantity, of route of infection, and of local conditions of development are often sufficient to explain differences in the character of the lesions. To be able to grasp with certainty the meaning of a difference in the reaction of the organism, it is necessary to know a great deal about the stimulus that provoked the reaction. The bacillus must be seen if one is to speak of the reaction of the host to it. Before one can evaluate with certainty an effect of allergy it is necessary that equal quantities of bacilli be found in different lesions, or unequal quantities of bacilli in similar lesions, or the absence of bacilli be established in lesions unquestionably tuberculous in origin. The bacillus is witness to new potentialities of reaction in the host. It provides the constant by means of which variations in its reactivity can be measured. To attempt an interpretation of these variations without knowledge of the fate of the bacillus can be likened to an attempt to solve a problem of two unknowns with one variable.

What is true for the concept of allergy holds also for many others. There is, for example, a widespread tendency among specialists in this field to explain everything in terms of the susceptibility or resistance of the host. Initial infection, extension, generalization, regression, cure—all are supposed to be dependent on factors affecting the organism as a whole. Whatever the forces involved (hereditary influences, nonspecific factors, variations in allergy, variations in specific immunity), they are always assumed to concern the organism as a whole. What an exag-

gerated point of view! Consider the bacillus in the lesion, experiencing such different fates in various foci of the same patient, and the same fate in widely different patients; destroyed in a certain histologic reaction and thriving in another nearby; swarming not by virtue of some mysterious force but simply because it is situated at a site from which swarming is possible (on the surface of a canalicular system); growing rapidly in certain necrotic areas and poorly in others; finding a proper environment only in certain tissues; slave of favorable conditions of oxygenation, and of the availability of subtle growth factors. How futile general explanations appear in this light! One cannot help being impressed by the existence of multiple local factors, by the importance of certain momentary conditions of bacillary metabolism and cellular susceptibilities—a constellation of complex, changing, and often incomprehensible circumstances limited in space and in time, and of which the host-organism remains ignorant. For it is false to believe that the host-organism possesses a kind of intuitive knowledge of all that occurs within it, and always possesses dictatorial power. It is quite possible that the overwhelming complexity of tuberculosis is due to the numerous factors that are not under direct control of the host (for reasons to be discussed later) in contrast to typhoid, diphtheria, and most other infections in which local conditions are of so much less importance.

The inadequacy of general explanations is due to another factor—chance. There is hesitation in acknowledging chance in scientific matters. Yet it is found everywhere, making sport of the efforts of reason. Chance plays a role of considerable importance in tuberculosis. Consider, for example, the softening of the caseum. In a cervical node, softening of the caseum leads to draining scrofula—a benign affair—but in the lung it is a disaster, for it means a cavity. Initial differences of organic susceptibility are of little relevance here. Indeed draining scrofula is seen more frequently in races with poor hereditary resistance and in subjects without specific immunity. Chance, determining the localization of the lesion, is interposed between the initial resistance of the subject and the terminal fact, the gravity of the disease. Chance is not intended, of course, to account for the absence of cause for each of the phases from beginning to end, but for the irrationality and total unpredictability in their concatenation. Multiple examples of this sort could be cited to prove the necessity of studying each lesion in all its pecularities.

In addition to the problem of allergy and the vanity of general explanations, a last example will be considered to demonstrate the necessity of histobacteriologic investigation—the problem of virulence.

In this domain, it is bacteriologic exclusivism instead of histologic exclusivism that has led us astray. Although certain authors (Boquet, Saenz) attribute virulence to the chemical and physicochemical properties of the bacilli, the general tendency is to see in it an expression of the aptitude of the bacillus to multiply in tissues. This interpretation does not exhaust the problem and is even somewhat irrelevant. It is true that the bacillus multiplies in the tissues of receptive species, but its pathogenic action—and this is what is implied in the term virulence—is not adequately explained by the extent of multiplication. Were it not for the habit of separating the study of the bacillus from that of the lesion, two fundamental facts would have struck investigators: On the one hand, the number of bacilli after an initial increase *diminishes* progressively as the lesion evolves, suggesting that a long and critical phase of the tuberculous process results from a destruction of bacilli and not from their multiplication. Comparative pathology, on the other hand, reveals that in species susceptible to tuberculosis, that is to say species in which the bacillus is very virulent (e.g. man, cattle), the lesions may contain at times only very few bacilli, whereas many may be found in the lesions of resistant species (dog, cat, horse). This paradoxical finding demonstrates that the ability of the bacilli to multiply in the tissues is not a sufficient determinant of their pathogenicity, although it is of course a necessary factor. All these notions, which will be more extensively examined in the course of the present study, make clear the importance of histobacteriologic analysis for a proper orientation in problems of pathogenesis.

Technical as well as doctrinal reasons are responsible for the neglect of histobacteriologic investigations in tuberculosis. First is the fact that pathologists are not necessarily bacteriologists and vice versa, and that their curiosities tend to become compartmentalized. Then comes the difficulty in seeing the bacilli in histologic sections, or the structure of the lesion in preparations stained to render the bacilli visible. Either histology or bacteriology is sacrificed in the staining process. However, these technical difficulties can be mastered readily if the problem is formulated with enough care. But the histobacteriologic problem has been shielded from the limelight by other types of investigation. In this respect, a rapid historic review is very revealing. The first and best studies of bacilli in sections were those of Koch and his contemporaries Herard, Cornil, Babes, and Baumgarten. Little has been added to their findings. But the question in the minds of these investigators should be clearly understood. They wanted to ascertain whether the bacillus newly discovered in the lesions of man was found there regularly. The problem was that of establishing

definitively the etiology of tuberculosis. The great debate on the unity or duality of tuberculosis, that is, whether infiltrative and nodular lesions could have the same etiology, was at its peak. The French school remained in general loyal to the unitarian interpretation of Laennec, while the German school, for the most part, adopted the dualist interpretation of Virchow who considered infiltrative lesions different in etiology from the nodular, true tuberculous lesions. The discovery of the bacillus settled this quarrel in favor of Laennec. But the etiologic preoccupations of the time gave a very special orientation to histobacteriologic studies. Little thought was given to problems of pathogenesis.

Among other histobacteriologic studies in the following years one must mention those inspired by Metchnikoff (Yersin, Borrel) as well as those of Baumgarten. They dealt with experimental and not with human tuberculosis. However, what relationship is there between the massive tuberculosis of experimental intravenous infection and the tuberculosis of man? Where in man does one see giant cells teeming with bacilli as shown in the often reproduced drawings by Koch and Borrel? One should never forget the limitations of experimental studies in animals. They provide useful hypotheses and certain facts not observable in man, but in no case can they replace observations in man for the ultimate understanding of the disease in human beings. This is particularly evident in the histobacteriology of tuberculosis. It is well known that different species react differently to the tubercle bacillus. Hence, the important differences found with reference to the histologic responses in a given lesion, and to the fate of the bacilli which they contain. It is in man that one must study the histobacteriology of human lesions, with the understanding that comparative studies on other species may, by analogies and differences, yield invaluable information.

The grossly bacteriologic era of 1890 to 1900 was followed, about 1905, by the immunologic era. In tuberculosis the main endeavor of this period was to explain everything by successive changes in the mode of reaction of the host. This tendency reached its extreme and was schematized in Ranke's theory. Even authors hostile to its excess accepted the main concept—credit for which belong to Behring and Roemer and not to Ranke—which considers as the determining factor in the course of a given case of tuberculosis the presence or absence of previous tuberculous infection. The division into primary infection and reinfection, proposed by Aschoff and universally accepted, is its most moderate expression. It is readily understood that the interest of histologists and pathologists was, at that time, focused on the changed reactivity

of the host and not on its cause. Hence, the long neglect of histobacteriologic studies. There is one remarkable exception to this general neglect. Bezançon, a pioneer in this domain, never ceased to proclaim the importance of the histobacteriologic point of view and patiently attempted to assemble information relevant to it. The remarkable study of the tubercle bacillus in the softening caseum made by Long in the United States, should also be mentioned. He described clearly the rapid multiplication of bacilli in these areas and called attention to the major importance of this phenomenon in the spread of tuberculosis. In Japan, Takeuchi extensively investigated the mechanism of bacillary destruction in tuberculous tissue and emphasized the role of the leukocytes as destructive agents. However, these studies did not receive the recognition they deserved because the times were not favorable. The introduction of antimicrobial drugs is likely to bring them to the limelight.

It is my pleasant duty to thank those who have made this work possible. I owe my interest in the subject to the teaching of Professor Bezançon. Professors Pasteur Vallery-Radot and Trefouel have given me their support and have permitted this volume to appear under the sponsorship of the Pasteur Institute. I express to them my gratitude. To my teachers at the Pasteur Institute, Drs. Boquet and Saenz, I am indebted for constant aid, encouragement, and much invaluable advice. I could not thank them sufficiently. It was in the laboratory of Professor Ameuille that I performed the autopsies and histologic investigations described in this study. Professor Ameuille has given me such constant help, critical judgment, and protection against obstacles, that this work is in part his. It is a debt of honor to recognize this heritage and a joy to express my gratitude to him. The sections studied in this work were prepared by Miss D. Grimaldi. Great skill was required to render the bacilli clearly visible, and I thank her for her efforts. The microphotographs were prepared by Dr. Mangini of the Cancer Institute. Thanks to his care, none needed to be retouched.

I am not unaware of the great imperfections and incompleteness of my work. The histobacteriology of extrapulmonary tuberculosis and that of nonhuman tuberculosis remain to be investigated almost in their entirety, but these developments will come rapidly if the importance of systematic histobacteriologic analysis is well understood. It is to contribute to this understanding that I have written my book, in the hope that its merit will prove to be the stimulus for more thorough study.

CHAPTER ONE

HISTOLOGY OF PULMONARY TUBERCULOSIS: A REVIEW

The subject matter of this work is not a detailed histologic study of pulmonary tuberculosis. Yet, as the lesions in this disease are essentially polymorphic, it is desirable to review the development and course of the tuberculous lesion before describing the behavior of the tubercle bacilli in them. This review is even more necessary because our concepts of the histology of pulmonary tuberculosis have undergone important changes in the last twenty years.

The study of the histogenesis of tuberculous lesions was undertaken in 1928 by Huebschmann. It is well known that there are three large categories of tuberculous lesions. First, inflammatory lesions, characterized by vasodilatation, edema, fibrinous exudate, an influx of the elements of the leukocytic series (polymorphonuclears, monocytes, lymphocytes); they are grouped by Aschoff under the term "exudative." Second, cellular metaplasias; monocytes from the blood and local histiocytes are transformed into epithelioid cells which in turn may be transformed into giant cells. These epithelioid cells are often, but not always, arranged in a rounded formation called the tubercle. This reaction, in conjunction with the subsequent sclerosis, is termed by Aschoff "productive." Finally, there are the caseous lesions, including the necrosis of turgescence and homogenization, which may sometimes soften.

From the classic point of view, the tuberculous process is supposed to begin sometimes with an exudative, and at other times with a productive lesion, with the subsequent occurrence of caseation at the expense of one or the other variety of lesion. Huebschmann has given an entirely different interpretation: Following an initial phase of "tissue damage," which is of uncertain duration and often poorly observed, the exudative reaction is the first clearly demonstrable phase of tuberculosis.

Caseation, the second phase of the lesion, proceeds at the expense of the elements of the exudative reaction as well as of the local tissue elements. Caseation is followed by the productive reaction: tubercle formation and sclerosis at the periphery of the caseum. The important concept introduced by Huebschmann is that he placed the exudative phase at the beginning of every tuberculous lesion, with tubercle formation *following* the occurrence of caseation. Certainly, subsequent aggravation of the disease may lead to caseation of the tubercle itself, but this secondary caseation is inconstant, usually incomplete, and cannot compare in importance with the earlier caseation.

This concept of histogenesis, elaborated upon in France by Delarue in his book on miliary tuberculosis, has not received the sanction of all pathologists. It has been criticized for denying the possibility of an initial productive reaction and postulating a constant initial exudation which is at times difficult to observe. These objections are not without foundation. Certain cutaneous lesions, for example, never show an initial exudative phase. In the horse the tuberculous process is always dominated by an almost tumoral proliferation of epithelioid cells, with little or no exudation and caseation. Each organ has its own peculiarities of reaction determined by its structure and each species its special susceptibility as manifested in the cellular arrangement of the lesion.

Besides, experimental evidence suggests that the initial presence of large numbers of bacilli is of paramount importance in giving an exudative character to a tuberculous lesion. But in spite of all this, the histogenesis described by Huebschmann is the one observed most frequently in the *pulmonary* lesions of man, occurring in nine tenths of the active as well as in the latent lesions. The great merit of Huebschmann was to provide an exact and fruitful view of the pathogenesis of human pulmonary tuberculosis. We shall in the main adopt this concept but shall have to abandon it on several occasions. The details of the description which follows are in general accord with those of the classic authors (Letulle[a], Aschoff, Huebschmann, Pagel[a], and Delarue) but differ on several points. The present author bases his views on the results of 1500 autopsies of tuberculous individuals performed during seven years in the laboratory of Professor Ameuille, and on the histologic examination of sections from large numbers of these cadavers. All findings were correlated with the clinical and radiologic record of each patient.