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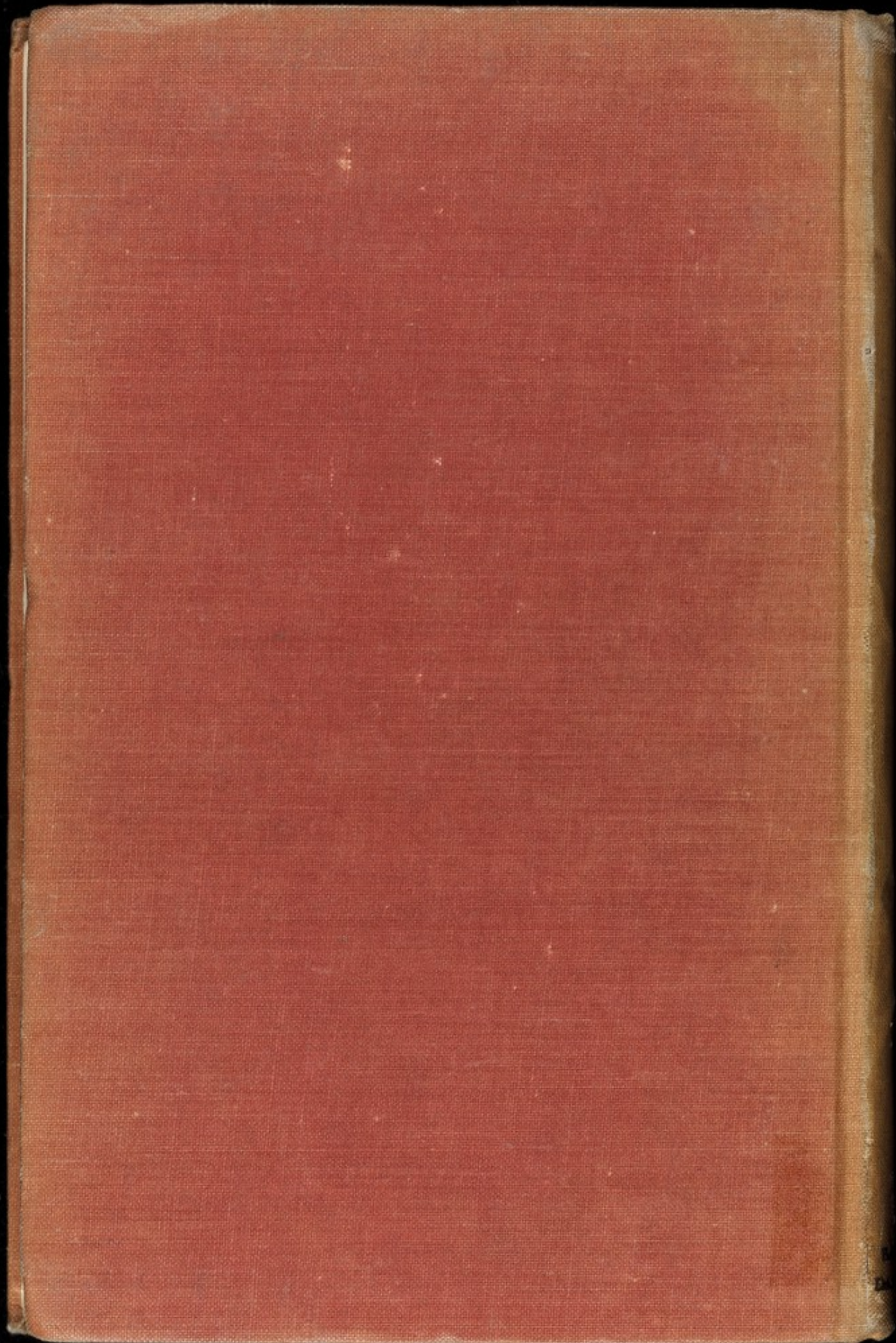
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TUBERCULOSIS

INFECTION—HEREDITY

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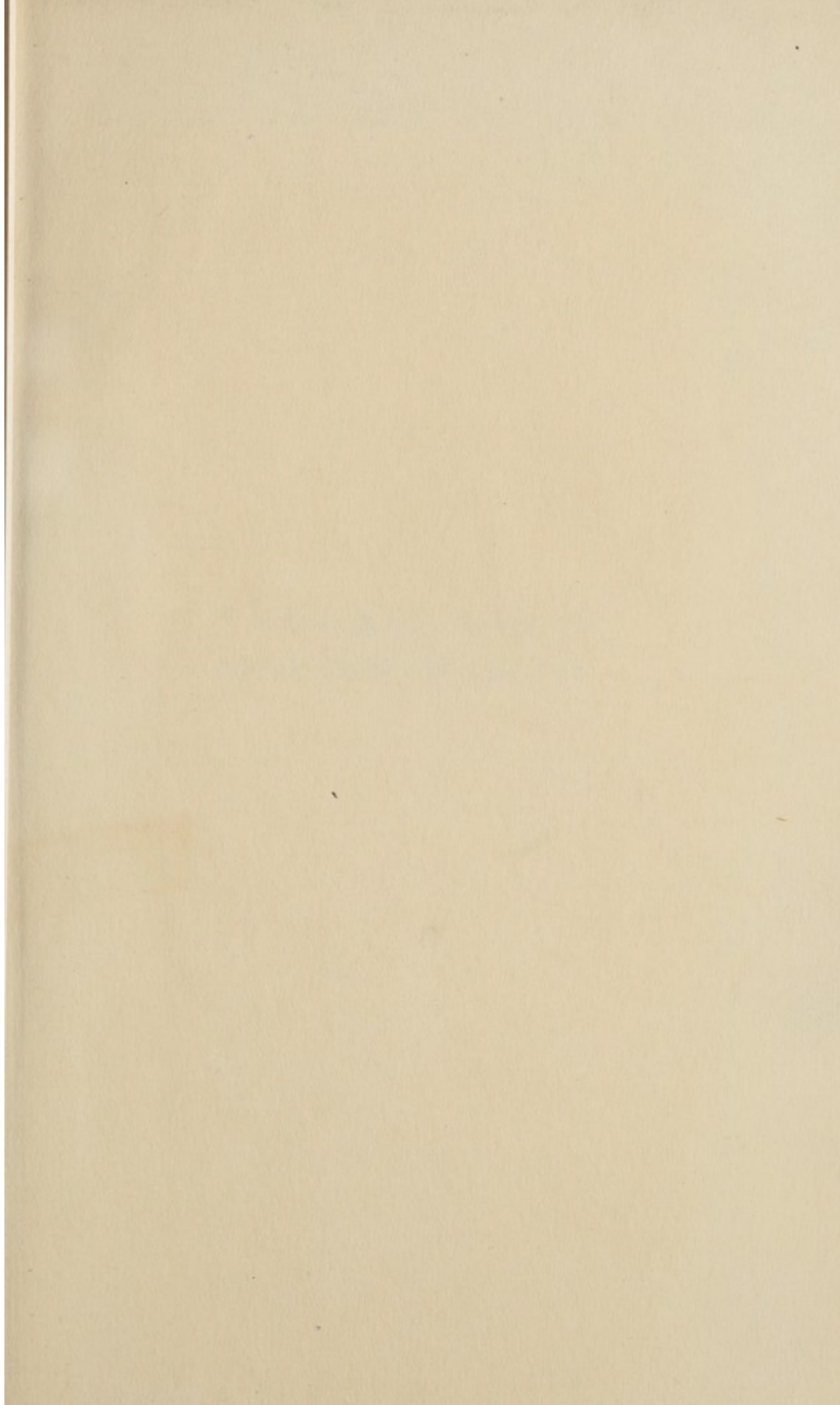
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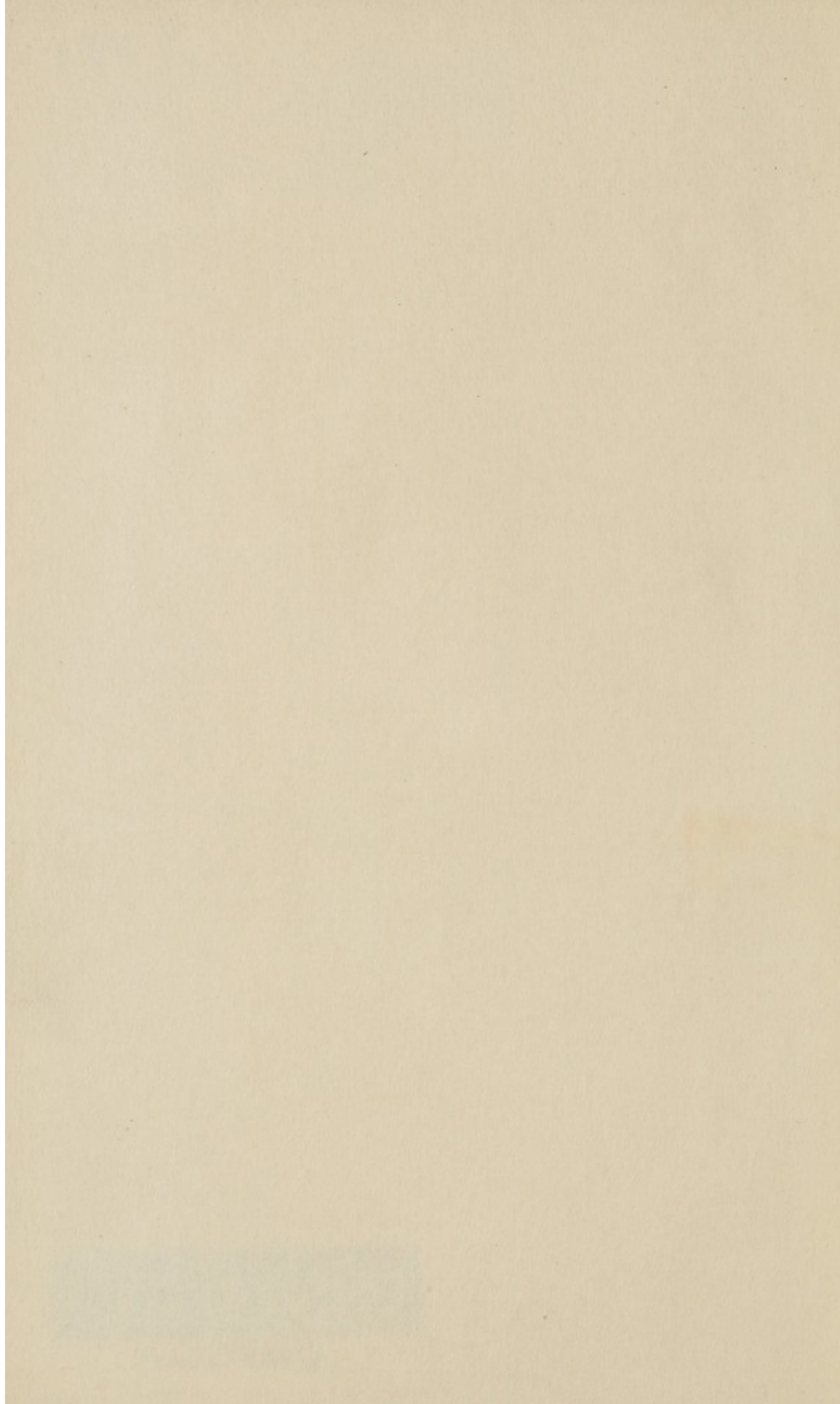


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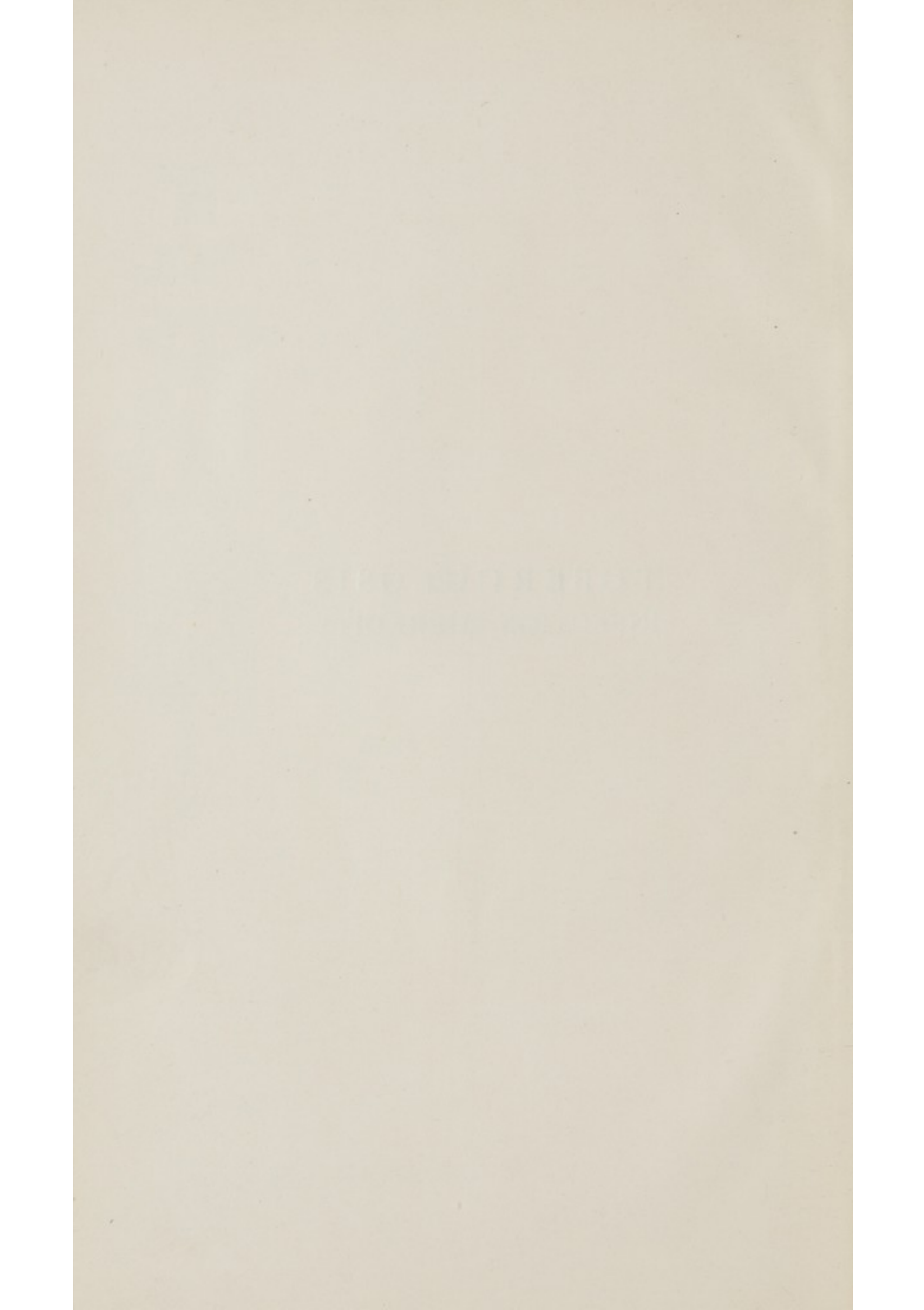


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TUBERCULOSIS
INFECTION—HEREDITY



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TUBERCULOSIS

INFECTION—HEREDITY

BY

AUGUSTE LUMIÈRE

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Correspondant de l'Académie de Médecine*

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PREFACE.

THIS book, "Tuberculosis: Infection, Heredity," first appeared early in June, 1930. I had been struck by the discrepancies which exist between the known facts and the classical or conventional theory that tuberculosis is not hereditary, but solely the result of infection. My purpose in writing this book has been to show that this theory, though it has been accepted for many years past, cannot solve the greatest problem of modern pathology, but is, on the contrary, questionable and inconsistent with many of the facts. By presenting this theory as finally proven and incontrovertible, may it not be said that pathologists have discouraged further research and thus hindered progress?

The views set forth in this book make no pretence of being unassailable. My purpose has been simply to re-open discussion on a question which is of paramount importance in medicine. I have expressed my own views as to the relative importance of heredity and infection in the propagation of tuberculosis, but I am perfectly willing, as I have pointed out repeatedly, to modify these views if their inaccuracy can be demonstrated to my satisfaction.

If I may be pardoned for paraphrasing the beginning of the first aphorism of Hippocrates, I would say that life is short, science the work of time, opportunity fleeting, experience deceitful, judgment difficult. I will go further, and add that the correct reading of facts calls for nice discrimination, for they are often liable to misconstruction. A scientist may fall into errors of technique or reasoning, and consequently should always draw inferences with caution, not seeking arguments in support of his views, but being ready to consider any objections to them. Once the simple explanation of a problem has been found it is easy to recognise the difficulties and complexities

which faced the observer, and to excuse him if he has been led into error. Such mistakes, when honestly acknowledged, are of considerable help to other investigators, and contribute their own share to the elucidation of the problem. Knowing how fallible he is and how he may be influenced by misleading evidence, the true scientist should remember that no quality is so valuable as that of readiness to admit an error. Nothing redounds more to his credit. His sole purpose should be the search for truth, even though the truth, when found, means the ruin of his aspirations and of the doctrines to which he was formerly attached.

It is my wish to follow this wise principle, and I shall have no hesitation in admitting that I have been mistaken if, at any time, I am led to that conclusion either as the result of my own investigations, or of the investigations of other writers.

With this end in view I have placed my book in the hands of some hundreds of members of the medical profession, including some of the most eminent consultants in tuberculosis, in the hope that my views might be discussed, and that the questions raised might take us further in the search for a solution of the enigma of tuberculosis. In the first edition of this book, by forsaking the orthodox view and expressing opinions at variance with the classical theory, I expected to raise a storm of protest against the heretic who had the audacity to believe that infection was not the sole means of transmission of this disease, the infidel who dared question the accepted creed.

At first I must confess to being disappointed. I received a number of kind acknowledgments of copies of the book, and some congratulations; a certain number of people seemed to endorse my views, and some even expressed unreserved approval, for which I take this opportunity of thanking them. But as far as criticism goes, I received none. Six months after publication of the book I had seen only one critical review, published in a newspaper, in which

an anonymous writer was good enough to offer a few objections to my conclusions.

Had I, then, failed to accomplish my purpose? Would this work be received with the same silence which has been maintained for ten years in official circles concerning my colloidal theory? Fortunately my friend, Professor Calmette, has been good enough to break through this ostracism and to offer my work a number of criticisms of the utmost interest. Although he does not share my views I am extremely grateful to him for giving them his consideration, thereby enabling me to advance a step further in the study of this distressing problem.

My satisfaction was increased when *La Vie Médicale* published an interesting inquiry into, and appreciation of, my work. Professors LEON BERNARD, CALMETTE, PIERY and SERGENT, Doctors F. BORDET, DUMAREST, GANDY, JACQUELIN, JOUSSET and STARLINGER, and finally Professors CONSTANTINI and RIETSCHER were good enough to answer the challenge of *La Vie Médicale*. I should like to take this opportunity of expressing my sincere gratitude both to the editors of that review, and to Dr. MORHARDT who summarised the opinions of these eminent authorities.

* * * * *

It is with regret that I attack the accepted doctrine, and I can well understand that medical men who have supported it throughout their professional lives will be reluctant to forsake it now. Such supporters of the accepted view can legitimately put forward every possible argument in its favour; such opposition favours the study and advancement of the problem. It is from a conflict of opposite theories, from the clash of opposed views, that the most accurate solution of a problem is often achieved. The stronger the resistance offered to a new theory the greater the service rendered to truth, for the exponents of the new view are compelled to proceed with caution

advancing only a step at a time, and making sure of their ground as they go.

I find it a painful duty to put forward this belief in the influence of heredity in the propagation of tuberculosis, realising, as I do, that I must cause distress to people who have suffered from the infection in the past and who have subsequently begotten a family.

"Your book demonstrates the influence of heredity," an authority on tuberculosis, who formerly suffered from the disease, writes to me. "This is most distressing for me, as I have children for whose safety I shall now feel anxiety." And another man accepts my views in the following terms: "I have read with dismay the powerful arguments you quote in support of the hereditary factor in infection, being myself an old consumptive and the father of a family. I do hope that the effects of heredity, though you have established their importance, are not unavoidable."

No, indeed, the effects of heredity are not unavoidable, and one is all the better able to evade them by being forewarned; rigorous sanitary and therapeutic measures can be taken early with a view to maintaining and reinforcing the patient's resistance. It is true, however, that I have had to make an effort to overcome my feelings in deciding to publish these conclusions, to which thought, observation and experiment have led me, for I realise that they are calculated to bring anxiety to the families of certain consumptive patients. It was not without some apprehension, or without due deliberation, that I entered upon a task through which I not only run the risk of disturbing those with whom I have the utmost sympathy, but in which I am likely to find my progress uncompromisingly blocked by a wall of classical opinion and convention.

I do not recoil, however, before these obstacles, because it seems to me that the search for truth is more important than any other consideration, however humane. The reader will, I think, find excuse

for me if he takes into account the terrible havoc wrought by tuberculosis. Every year one hundred thousand French citizens succumb to this disease, and several hundreds of thousands are tainted with it. It mows down the young before they have fulfilled their social duty. Throughout the world literally millions are victimised by it. The massacres of warfare, particularly of the present day, play havoc with the lives of mankind, but the total casualties of all the wars of the past are trifling compared with the innumerable victims claimed by tuberculosis through the centuries.

My wish has been to make a modest contribution to those investigations which will some day bring to light the long-desired truth. What is this contribution worth? The future will show. Meanwhile I can declare that I submit it in the utmost sincerity, and with complete serenity, believing my work to be free from the influence of preconceived ideas; in developing my theory I have endeavoured to adopt a rigorously scientific method, which has sometimes been difficult to follow without faltering. I do not pretend that I have never departed from it at all, and it is in these involuntary lapses that such defects as are present in this thesis may be found. Whatever the final judgment of my book may be, I believe myself to have done useful work in devoting myself whole-heartedly to this self-imposed task, because it aims at the solution of the most important problem which concerns mankind.

* * * * *

It is of material importance that members of the medical profession, and all those who take an interest in this outstanding pathological question, should be informed of all the elements in the controversy which my work was designed to stimulate. For this reason, the first edition of my book being out of print, I felt that upon the issue of a second edition I ought to include those arguments—with my replies

to them—which have been brought forward against my theory, in order that the reader might make his final judgment in full knowledge of the facts. Unfortunately the criticisms levelled at my work have been all too few and too unimportant.

The writers who have disputed my views have, for the most part, expressed personal opinions, unsupported by proof, and in no sense have they replied to my objections to the conventional theory. They failed entirely to explain away the discrepancies which I had pointed out between the known facts and the accepted interpretation of them. The criticisms most frequently made had no bearing on the facts themselves, but were levelled at my clinical competency, my working methods, and the processes I have adopted in order to study the problem.

Although criticisms of this kind do not affect the merits of the case, I have included them in a chapter at the end of the book.

It will behove the medical profession to find a verdict.

LYONS,

January, 1931.

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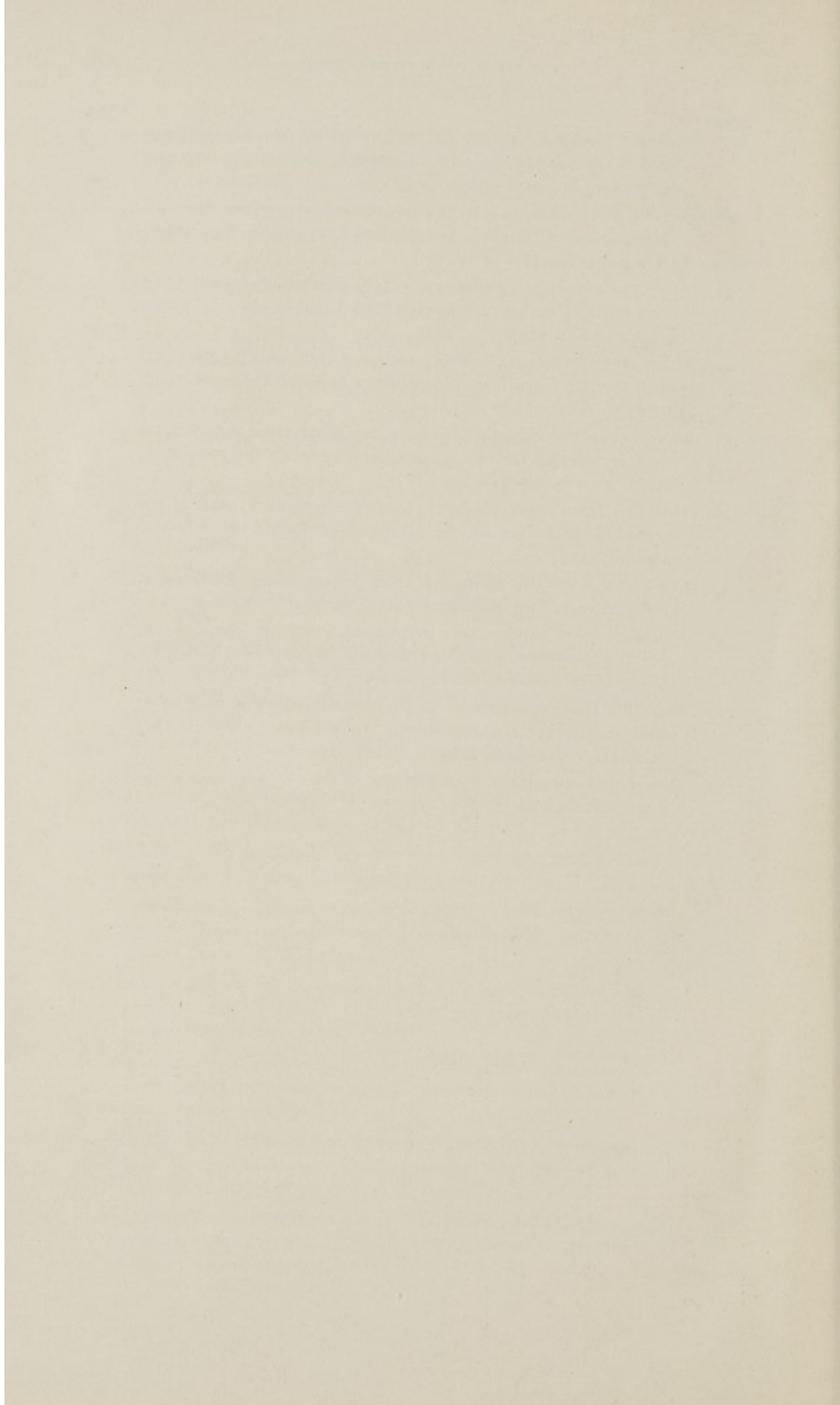
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INTRODUCTION.

AT the present time tuberculosis seems to be the worst disease which attacks mankind. The work of investigators all over the world has resulted in the publication of a mass of literature on the subject, so that it has become almost impossible to draw up a complete bibliography; few physicians have failed to make a contribution of some kind to the study of this widespread and protean disease. If my purpose had only been to classify modern theories of the disease, and to comment on them, I should have felt chary of increasing the literature on this subject. I do not, however, propose to follow the trail blazed by the medical profession, but to diverge from it as much as possible. We must explore fresh paths if we are to advance our knowledge of tuberculosis.

It cannot be denied that valuable progress in the bacteriology of the disease has been made during the last fifty years: the observations of Koch, Villemin and Calmette have proved the starting points of new lines of research; the outcome has been the evolution of theories which are now generally accepted as facts. The view is taken that tuberculosis is not hereditary, that spread is chiefly by infection; that apart from some method of collapsing the lung no specific form of treatment exists; that nothing is to be gained by trying to reduce the hectic temperature in tuberculosis; and that a sanatorium régime is the only thing likely to be effective in the treatment of those cases which are not suitable for treatment by artificial pneumothorax, thoracoplasty or phrenicotomy, or who have not already benefited by such measures.

If we accept these dogmatic views we must assume that finality has been reached in the study of tuberculosis; every stimulus to research is destroyed. Dogma in science! Could there be any greater

hindrance to progress? Dogma is essentially opposed to science because science must remain fluid, its conclusions provisional. Should it not be admitted that such formulæ are only partly true, that errors have crept into the textbooks, that many of our inferences must perforce be doubtful and inaccurate, and that the accepted views, copied from one textbook to another, call for revision? Many a medical practitioner, as a result of his literal acceptance of textbook doctrines, will explain the painful symptoms of a patient as being due to the rheumatic diathesis, and feel satisfied with that diagnosis; or, when faced with one of the dermatoses, he will prescribe some complicated ointment, which is likely to have little effect on a condition which is not of superficial origin.

I do not question the ability or knowledge of doctors, but only their method of approach to medical problems. From the early days of their training and throughout the medical curriculum they are taught accepted theories which destroy the faculty of doubt, the importance of which is so justly emphasised by Claude Bernard in his "*Introduction à l'étude de la Médecine expérimentale*." Doubt, however, is the chief incentive to scientific research, and an important element in the advance of knowledge.

The purpose of this book is to counteract the effects of dogma as far as the problems of tuberculosis are concerned. I should like to feel that a doctor, when someone stated in his presence that tuberculosis was not hereditary, would reply: "That may be true, but one cannot be sure about it; so far it has never been demonstrated beyond question."

Attempts might then be made to demonstrate the influence of heredity, and if no evidence in its favour could be obtained there would be grounds for attaching credence to the accepted theory. Until this is done a wide field of study must remain unexplored. I was not without misgivings when I undertook to attack the conventional view in this book. I doubted whether I was sufficiently informed to undertake such a

critical study, or to raise my voice against admitted principles. When I came to consider, however, that for a good many years I had been undertaking experiments—most of them original—with Koch's bacillus and its toxins, and with animals infected with tuberculosis; that I had had the opportunity to observe the course of the disease in thousands of cases; and that I was widely read in the subject of tuberculosis, it seemed to me that I was qualified to undertake a task which could not fail to be of some use.

I have made no attempt in the following pages to discuss all the theories of tuberculosis: I have limited myself to an unbiased examination of the influence of infection and heredity in the propagation of the disease, reserving for a second book the study of other classical doctrines, beginning with those relating to treatment. If I have managed to bring to an end—I will not be so presumptuous as to say a successful end—this self-imposed task, I am indebted for it to my usual collaborators and to various friends in the medical profession who have given me valuable assistance in different branches of my work, notably Doctors VIGNE, BOUQUET, GAUDON, BOISSEL, H. MOLLARD and LEONET; Prof. NOEL; MM. CHEVROTIER, BOURGEOIS and BOURJON; Mme. DUBOIS; and Mdles. ROCHE-BILLARD and FAVRE. I wish to express my sincere thanks to them for the help they have given me.

HOULGATE,

July 27, 1929.

CHAPTER I.

FLUCTUATIONS OF MEDICAL OPINION IN THE PAST.

AUTHORITIES on tuberculosis at the present time hold the view that the disease is transmitted by infection. It is assumed that the infant is born free of tuberculosis and can only contract the disease by infection with the organism, either by way of the respiratory system or, more commonly, by way of the intestinal tract. Before this conclusion was reached medical opinion wavered considerably, and, at some periods, diametrically opposed views were current. It may be as well to summarise the course of the controversy.

No indication of a belief in infection is to be found in the writings of HIPPOCRATES. The immortal physician of Cos said: "A consumptive is born a consumptive." Yet in Greece, shortly afterwards, phthisis was considered to be infectious. We read in "Æginetic" of ISOCRATES that a man, having visited a consumptive who had made him his heir, was in such a poor state of health that his friends advised him to be careful, since *most of those who nursed this disease fell victims to it.*

ARISTOTLE endorsed this opinion in his "Problems." To the question, "How is consumption acquired?" he replies: "From propinquity; phthisis makes the inhaled air noxious and foul."

During the course of the fifteenth, sixteenth and seventeenth centuries, further observations were made; the tuberculous lesion was first described by SILVIUS, and attention was once more directed to the hereditary

factor by VAN HELMONT, FRACASTOR and BOERHAAVE, who noted that children of consumptive parents were likely to succumb to the same disease.

Later still, opinions were divided. MORTON, SENNERT, VALSALVA, VAN SWIETEN, PORTAL, ANGLADA and BAUMES attributed spread of the disease to infection, while others, by comparing facts, classifying observations and studying the course of the disease, arrived at the view that phthisis was the result of persistent damage to nutrition.

"Tuberculosis," PETER held, "is evidence of a decline of the whole system."

Nearer our own day, the theory of heredity recovered its prestige in the teaching of the great nineteenth century physicians, LAENNEC, ANDRAL and TROUSSEAU.

"Phthisis," LAENNEC wrote, "has long been accepted as being due to infection, and this view is still held by the public, by magistrates, and by a few medical men, and is current in certain countries, especially those of southern Europe. In France, at all events, this theory does not seem to be tenable."

It must be admitted, however, that these eminent clinicians doubted whether the theory of infection could be entirely rejected. They joined with LAENNEC in advocating "precautionary measures for those living with consumptives, especially if the disease is advanced, since the exhalations of the body cannot fail to be injurious to health."

GRISOLLE wrote: "We believe the fear of infection to be groundless." He had seen, however, a number of women, with no family history of tuberculosis, die from consumption, although they had passed the age at which the disease is most likely to be serious, and he added: "Are such cases the result of infection? Or may something be ascribed to emotional disturbance such as grief and exhaustion or to privation or chill? Devoted wives often sleep with the sick man until the time of his death, rising at any moment to attend to his wants, although they may themselves

be bathed in sweat, and liable to take a cold which is the forerunner of an organic lesion."

In spite of these discreet reservations the cardinal importance of heredity in the transmission of the disease was so generally accepted during the last century that REQUIN wrote in 1854: "Nowadays, when the theory of infection has scarcely a supporter in England, Germany or northern Europe, those of us who are making contributions to French medical literature have no need to attack this particular bogey."

PETER, meanwhile, had adopted a new conception. "It is not the disease but the tendency which is hereditary," he contended. "Children are not born tuberculous; they are born liable to acquire tuberculosis. . . . If phthisis was infectious discussion would have come to an end long ago. Everyone would have been convinced by weight of evidence, for, of all diseases, phthisis surely ought to be the most infectious; the prolonged course of the illness ought to facilitate the spread of infection to thousands of people. A single case of variola can give rise to some hundreds of return cases inside a fortnight. If phthisis was infectious those who attend patients with consumption would readily take the disease, so that doctors, medical students and nurses would all be dead or dying."

TISSOT, PORTAL and FRANK, and later CHOMEL, GENDRIN, MONNERET, ROCHE and many others, took the view that tuberculosis was entirely the result of heredity, while other observers refused to accept this theory.

"It is a misfortune for any child to be born of tuberculous parents," said BOUCHARDAT, "not because he has tuberculosis at birth—a rare occurrence—but because he inherits the tendency, tastes and habits which led his parents to develop the disease."

In VIRCHOW's view: "the constitutional weakness which, in the parents, previously gave rise to disorders of various kinds, induces an innate tendency to tuberculosis in the children."

Indeed, the view held by REQUIN and most of his contemporaries was not really so universally accepted as he would have us believe. SANGALLI, in Pavia, denied the influence of heredity and, at the same time, VASHE was trying to minimise its importance. Regardless of the scorn of contemporary authorities a small number of physicians clung to the theory of infection. BERNARDEAU, THOLOZAN, MICHEL LEVY, BONNET, DE MALHERBE and GUENEAU DE MUSSY were of this number.

HARDY, addressing the Academy of Medicine, said : "I know that the facts in support of the theory of infection are few, and, moreover, have never been collated. Every practitioner can call to mind three or four of them, but if someone would take the trouble to assemble such scattered observations we should reach a result of some value."

Shortly afterwards, CORNIL, BOUCHARD, SEE, JACCOUD and POTAIN came round to the same view ; and MUSGRAVE-CLAY, in his inaugural lecture, referred to a number of cases of tuberculosis transmitted by infection, quoting especially from BRUCHON, GUIBOUT, VIALETES, ROUSTAN, BERGERET D'ARBOIS, LANCEREAU, COUPIN, BERNARD and others.

This return to the theory of infection received additional impetus from the memorable experiments of VILLEMEN, who, in 1863, demonstrated conclusively that tuberculosis could be transmitted by inoculation of caseous material from tuberculous lesions.

Nevertheless, during the golden age of medical science, which was just beginning, though new and fertile fields of study were opened up, theories of the ætiology and pathology of tuberculosis were influenced by the fact that attention was especially directed towards bacteriology and infection. The discovery of the tubercle bacillus by ROBERT KOCH in 1882 brought considerable support to these theories. Once the organism had been isolated, various animal experiments became possible, which tended to confirm the theory of infection. Tuberculosis was

formally recognised as an infective disease, and the part played by heredity was regarded as negligible.

"Nothing can be done to conquer tuberculosis," CHAUVEAU asserted, "until we declare war to the death upon the infecting organism."

The whole of prophylaxis was thenceforward directed against the tubercle bacillus, the scapegoat responsible for all the trouble! These views inevitably carried conviction, not only among doctors, but among the community at large. Upon them the accepted theory is founded.

Whenever a great discovery is made, there is a tendency to see in it the explanation of every problem connected with it, however remotely; every other consideration is lost to sight. The conclusions reached are exaggerated and extreme, and do not fall into their proper perspective until the early enthusiasm has died down, or until new facts come to light to moderate them.

The fluctuations of opinion over scientific problems, prior to their final solution, can be explained in this way. As far as tuberculosis is concerned, the swing of the pendulum has been wide. The accepted view of 1856 differed from that of 1920, as well as from the views current in earlier centuries—while those, in turn, were opposed to the view held by the ancients.

In the accepted modern view—that tuberculosis is transmitted only by infection—have we reached ultimate truth? I do not think so for a moment. We have only reached another peak in the fluctuating curve of scientific opinion, and I believe that here, as elsewhere, the old tag: "*in medio stat virtus*" may be profitably applied.

I admit that some courage is needed to lift one's voice against a doctrine which has, so to speak, no detractors. It requires far less courage, however, than that shown by Dr. P. JOUSSET, who, as early as 1907, attacked the accepted theory in a remarkable work¹ to which I shall have many occasions to refer.

¹ P. JOUSSET. "La Prophylaxie dans la Tuberculose." Paris: Baillière et Fils. 1907.

Though the views he put forward have evoked no response, most of the arguments he adduced in support of them remain unrefuted. While I am far from adopting all his views I hope to be able to produce facts in support of most of them. I trust to show, above all, that if infection is by no means negligible in the transmission of tuberculosis, the part played by heredity cannot be denied, in spite of what the textbooks tell us. In the chapters which follow it has been necessary to consider every fact from two aspects—from the point of view of infection and the point of view of heredity. This has entailed a certain amount of repetition which I hope the reader will excuse.

CHAPTER II.

CLINICAL AND DOCUMENTARY EVIDENCE OF TRANSMISSION OF TUBERCULOSIS BY INFECTION.

THE belief in the theory of infection is based upon two groups of facts : upon clinical observations and statistics, and upon experiment. I shall try to analyse and interpret as rationally as possible the arguments based on these facts, refusing to accept without discussion the hasty conclusions usually drawn from them. This chapter will be devoted to the consideration of clinical facts and statistics.

(1) *Infection in Adults.*

In order to ascertain whether tuberculosis is transmitted by infection from one grown person to another we must consider what happens when an adult is placed in conditions favourable to infection. Those especially exposed to infection are : (a) wives or husbands of consumptives who take no precautions against infection and often share the same bed as the patient for many years ; (b) physicians and nurses staffing sanatoriums, who are constantly in contact with patients coughing up tubercle bacilli in their sputum.

The repeated opportunities for infection which these two groups of people encounter, and the long periods of exposure—lasting in the case of some medical men for as much as half a century—suggest, *a priori*, that if tuberculosis were infectious very few such persons could escape it. This is not the case when those contacts who have a family history of tuberculosis are eliminated, it is found that the others,

in whom the hereditary factor may be presumed to play no part, will tolerate prolonged exposure to infection without falling victims to the disease.

What arguments are usually quoted in favour of the view that infection is a factor of importance between married persons, and between the patients and staff of sanatoriums?

Infection between Married Persons.

I am frequently asked: "What about conjugal tuberculosis? Every doctor meets cases of the kind. But since the patient is an adult the disease is not always fatal; his resistance is sufficient to conquer the disease. He is never included in the statistics of the death-rate from tuberculosis, but every experienced practitioner encounters such cases."

Before declaring that such a patient has been infected with tuberculosis by his wife the practitioner does not always take the precaution of ascertaining whether there is any family history of tuberculosis, much less of examining the parents of the patient, clinically and radiographically, for evidence of the disease. Even if he is willing to carry out such an investigation, it is often impossible to do so—the parents may have left the neighbourhood—and inquiries of the kind are costly as well as lengthy. The practitioner can hardly be expected to bear the expense of the investigation for the love of his art, and he cannot well charge the patient for it. Moreover, a good deal of tact is needed if inquiries are to be undertaken without alarming the parents and relatives of the patient. It is clear, however, that in the absence of such thorough investigation, evidence of infection between husband and wife cannot be accepted as reliable. I quote a typical case history which is supposed to demonstrate the occurrence of conjugal infection.

Case History.—Mr. X, son of a tuberculous parent and suffering from the condition himself, married

Miss Y, daughter of healthy parents, who was in perfect health at the time of her marriage. After a few years the wife became consumptive and died.

It was assumed that she had acquired the infection from her husband. In nearly every case assertions of this kind are entirely unsupported. In order to lay the blame upon infection rather than heredity, or a hereditary predisposition, it would be necessary to be certain that the wife's family were really free from tuberculosis. But there are few cases in which such an assurance could be given without arousing scepticism among clinicians.

What constitutes hereditary tuberculosis? How is the family history generally obtained? The interrogation usually runs as follows :—

Doctor. Are your parents still living?

Patient. My father died at the age of 42 from the results of an accident (or from an acute disease).

Doctor. Had he been a healthy man until then?

Patient. He never had a day in bed as far as I know. He was perfectly healthy.

Doctor. And your mother?

Patient. My mother is 54, and is perfectly well.

Doctor. Have you any brothers or sisters?

Patient. I am an only son (or I have a brother who is quite well).

Following which catechism the doctor puts down in his record: "No family history of tuberculosis." As a rule he is convinced this is the truth, though nothing could be more uncertain.

For one thing the parents are often unaware of being tuberculous; to accept their statements is to run the risk of falling into gross errors, as the following example shows :—

A young man, aged 20, suffering from active, bilateral, fibrocaceous tuberculosis, was transferred from a Lyons hospital to the Bon Abri private hospital at Villeurbanne, where he was to receive the gold salts treatment. His record card stated that there was no family history of tuberculosis, and his

parents, who accompanied him, declared formally that they had always been healthy and that the boy's brother was robust, and in excellent health. The mother, who refused to leave the bedside of the patient, shortly afterwards developed influenza and came under medical care. When examined she was found to have a scoliosis, the result of old Pott's disease. The deformity had developed insidiously during infancy, and had passed unnoticed.

Another example is to be found in the case history of a son of one of my colleagues, with whom I had worked for 40 years. The boy developed Pott's disease and succumbed to generalised tuberculosis. It was difficult to see how the disease could have been acquired by a person so carefully supervised, whose parents, moreover, had every appearance of sound health. The father was never ill and had no cough—as I myself, being in constant association with him, could testify. By the merest chance, however, I had occasion, one day, to auscultate his chest, and found the right lung to be the site of a widespread fibrosis which had developed without causing symptoms.

If further examples are needed, I may quote the case of Miss H., aged 16, who came into the clinical ward attached to my laboratories in 1929. Her elder sister was in hospital at Hauteville, and had been there for six months, and the mother was anxious because Miss H. had been coughing for some time, and had grown pale and lost weight ; she had no fever, however, and no profuse sweats, her appetite was fair and her digestion good ; no albumin was found in the urine, and examination of the sputum for tubercle bacilli was negative. On physical examination, an impaired percussion note was found at the right apex ; expiration was slightly prolonged, and wheezing ; fine crepitations were audible over the whole of the upper lobe, front and back. On inquiry I was told that both parents had always been healthy and free from cough, and that there was no reason

to suppose they had ever suffered from tuberculosis. A month later the patient—who was being treated successfully with gold salts—told me that her younger sister, aged 9, was suffering from cough and loss of weight. Examination of this child revealed the presence of enlarged glands at the hilum and of an incipient lesion of the right apex, confirmed by radioscopy.

Here, then, were three sisters suffering from tuberculosis, the disease having developed in the eldest at the age of 22, in the second at 16, and in the third at 9. Precautions had been taken to avoid transmission from one to another, but, in spite of this, those who hold to the theory of infection will have it that the disease was transmitted from one of the patients to her sisters, and that, indeed, had been the opinion of a medical friend of mine who had examined them. I pushed investigations further, however, and persuaded the parents to be radiographed.

Fig. 1 is a reproduction of the father's radiograph, and reveals the presence of a widespread fibrous lesion of both apices. I now succeeded in eliciting the story that the father had coughed up blood on more than one occasion, two or three years prior to his marriage, but that he had not found it necessary to give up his work as the trouble seemed to be trifling, the blood coming from his throat, as he put it. Eventually the family managed to remember that the grandfather of our young patients had died of consumption.

Parents are naturally reluctant to admit that they have passed on disease to their children; they find it painful to realise that in bringing children into the world they have condemned them to suffer from their own infirmities. By auto-suggestion they will persuade themselves that they were never ill in their lives and will state this as a fact to the doctor. Past illnesses are easily overlooked, or, if remembered, are dismissed as trivial.

One more case of the kind may be recorded. A



FIG. 1.—Neglected pulmonary tuberculosis. Fibrosis of both apices.

young man, Mr. N., aged 17, returned from his holidays at the end of September, 1928, and before returning to his studies came to see me, feeling, he said, "a bit fagged" in spite of his two months' rest. During his holiday in the mountains he had grown thinner, his appetite had been capricious, and he had developed a dry cough which had alarmed his parents ; there were no other symptoms. The parents, who accompanied him, appeared to be perfectly well, and stated that their health had always been excellent. The family history did not warrant any suspicion that the boy's condition was hereditary. Examination revealed fibrous lesions at both apices, especially on the right, and radioscopy showed a much enlarged gland at the hilum on the same side.

I persuaded the mother to submit to radiographical examination, and fig. 2 shows the condition which was revealed. Here again we have a case in which tuberculosis was present in one of the parents, the condition having developed in an apparently healthy woman with a high colour, without giving rise to symptoms or being remarked by her friends.

I could quote many similar cases which I have been able to put on record since I began to look systematically for evidence of hereditary transmission of tuberculosis; and every doctor could quote examples if his attention had been called to the importance of checking the statements of patients and their families. I need not labour the point ; I only wish to show that a note on the patient's record card, to the effect that there is no history of tuberculosis in the family, is seldom reliable, and should never be taken into consideration if founded on the statements of the patient or his parents, unless the parents themselves have been subjected to a thorough examination.

Apart from signs of latent tuberculosis which may be detected on auscultation, the parents may be suffering from a more obscure form of the disease. I refer to the benign, chronic type of tuberculosis to which Dr. DUMAREST has devoted papers in the

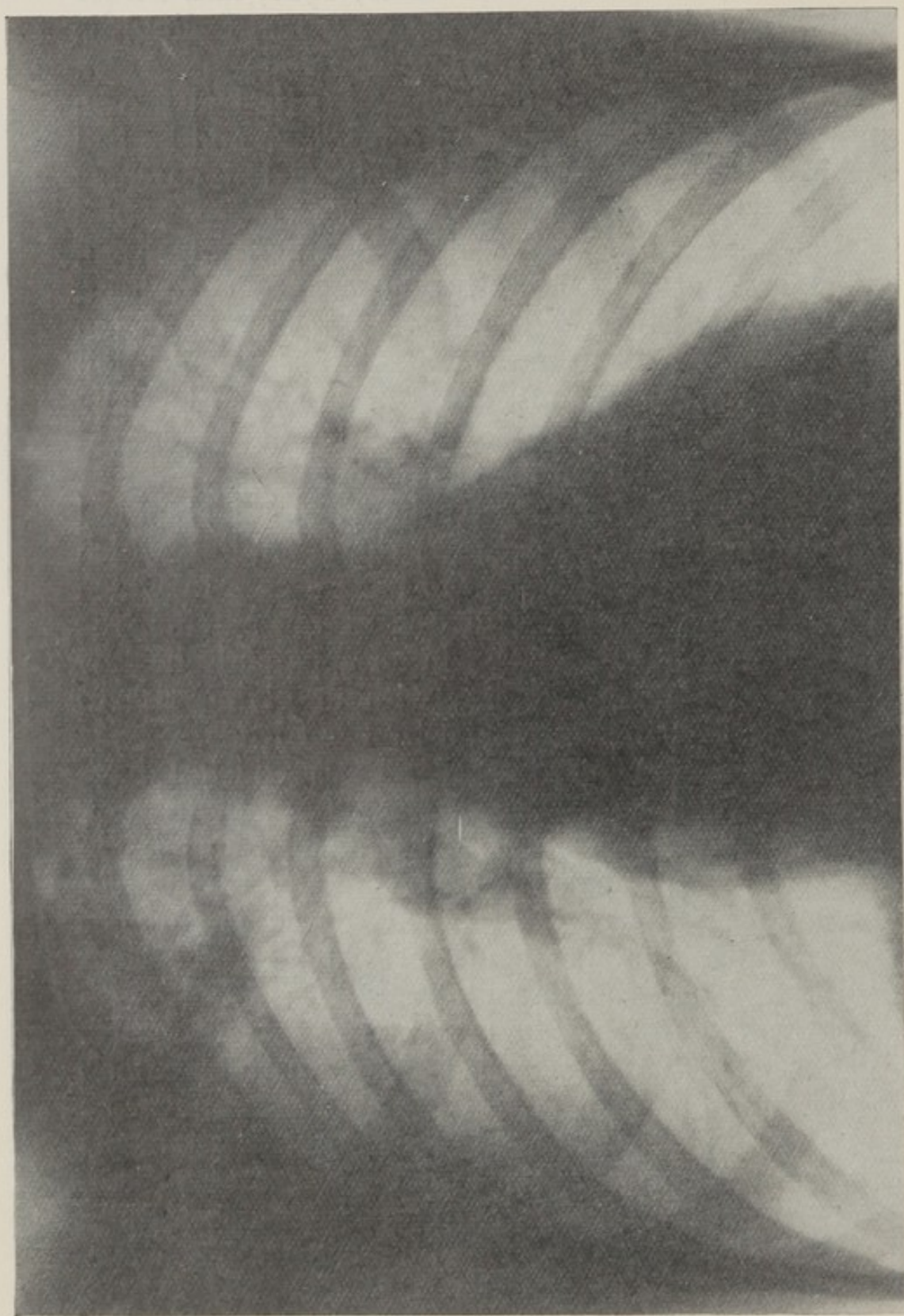


FIG. 2.—Neglected tuberculosis in a florid patient.

Medical Bulletin of the Hauteville-Lompnes Station,¹ and the *Lyons Journal de Medecine*.² Such lesions as peribronchial fibrosis, enlargement of the hilar glands, fibrous nodules in the lung parenchyma, which can develop without giving rise either to symptoms or signs, are apt to be overlooked by the medical attendant as well as by the patient and his friends. They are only detected by chance, on radioscopic examination. Unless the parents of a tuberculous patient have been examined radioscopically, no one is entitled to say that heredity can be ruled out of consideration. But how often is the patient's family history checked in this way? Almost never.

There is a third pulmonary syndrome, which, in my opinion, people connect too seldom with tuberculosis; I refer to certain forms of asthma and emphysema. Some writers even doubt the existence of asthma of tuberculous origin³. In my view, the proteins of the tubercle bacillus may produce, more often than is usually supposed, a form of anaphylactic sensitisation which is responsible for the onset of asthma; this view is supported by the fact that if one succeeds in desensitising the patient the asthma attacks stop immediately. Koch's bacilli, after being washed in ether and acetone to remove the waxy envelopes, may be made into an emulsion with glycerine and used as a desensitising agent. BONNAMOUR, DUQUAIRE and later BOISSEL, were able to cure many cases of asthma and to improve others by this treatment. Working with GELIBERT, I have also made use of this method, with successful results in more than three-quarters of the cases treated.

It must be regarded as significant, therefore, when a patient states that his father or mother is an asthmatic; although there is no actual proof, it may

¹ January, 1929, p. 47. "L'Evolution et le diagnostic de la Tuberculose pulmonaire chronique benigne."

² October, 1929, p. 649. "Sur le diagnostic radiologique de la Tuberculose pulmonaire."

³ L. SEDILLOT. "L'Asthme, uricémie respiratoire." Paris: Arnette. 1926, pp. 104-120.

be taken as strong presumptive evidence that the parent is tuberculous.

When the parents of a patient are dead the family history obtained will seldom be precise, and it is usually impossible to draw reliable inferences from it ; the patient's memory usually fails him, or else he draws erroneous conclusions from the facts he is able to recall, or again his parents may have died from accident, or from intercurrent disease which masked the symptoms of tuberculosis ; or they may have suffered from the latent form of the disease which passed unsuspected.

We may conclude, then, that the cases in which tuberculosis is said to have been transmitted between husband and wife prove nothing, because the hereditary factor has not been scientifically eliminated ; in none of the cases on record is there anything to suggest that the parents of a patient acquiring the disease were submitted to a thorough medical examination, including radioscopy. One cannot assert, therefore, that in such cases conjugal infection, rather than heredity, or hereditary predisposition, has been at work.

I have set myself, for several years now, to undertake just such conscientious examination of the parents in every case where the obstacles to investigation were not insuperable ; in every case where it has been possible to study, in this way, the heredity of an " infected " husband or wife I have found evidence of tuberculosis in the parents. Some day, of course, I shall encounter exceptions, but what will their significance be in face of the enormous predominance of positive cases ?

The most that can be said of infection in adults is that it is extremely rare.

I cannot understand, however, the view of those who pretend that tuberculosis occurring in the wife or husband of a consumptive is especially serious. The disease does not, in point of fact, differ from the usual type of tuberculosis in adults ; it is the same condition whether the patient is the wife or husband of a consumptive, or a bachelor or spinster.

(2) *The Value of Statistics.*

In his book on tuberculosis, published in 1899, JOUSSET records the deaths of 134 patients who acquired phthisis while married to consumptives; in 128 cases only one of the married pair succumbed, while the other survived for many years. In only 6 cases was tuberculosis responsible for the death of both patients. In a later investigation, made among working-class people attending dispensaries, the same observer collected a further series of 88 cases of conjugal tuberculosis; in 85 of these cases the disease was fatal to one partner, and, in 3 cases only, to both.

Other statistics point to rather different conclusions; among 402 cases collected for THOM at the Hohenhomef Sanatorium, both partners succumbed in 25 cases. Wide discrepancies are evident in the readings of statistics referring to conjugal tuberculosis, some authorities asserting that infection never occurs, and others that the majority of persons married to consumptives will sooner or later develop symptoms of pulmonary tuberculosis.

FISCHBERG records infection in only 3 per cent. of cases, while MINNING, BREKMER and HAUPT make the incidence 12 per cent., KIRCHNER 17 per cent., ELSAESSER 39 per cent., BARNS 2.20 per cent. (United States, 1921), and WARD makes it as high as 58 per cent. (England, 1919)!

ROBERTSON, in 1882, when communicating his observations on 100 families in his practice to the British Medical Association, said: "Out of 100 married couples in which one partner was consumptive the other partner remained sound in 80 cases; the children of consumptive parents escaped the disease in 69 cases out of 100."

In reply to an inquiry made among the members of the Italian Society of Hygiene, 680 letters were received; in 407 transmission of the disease was ascribed chiefly to heredity, in 59 the verdict was in favour of infection, and in 124 against it. At

the Congress held in 1905 MONGOUR reported the results of his investigations as follows: "Among 440 married couples of whom one partner was consumptive, infection of the sound partner occurred in 16 cases." In 1921, BRUNCH wrote: "Cases in which only one partner of a married couple suffers from tuberculosis constitute an overwhelming majority. During thirty years' practice I met only one case in which a husband and wife appeared to have infected each other. Negative observations have a value of their own, of which too little account is taken."

In an extremely interesting paper published in 1922,¹ P. ROUSSEL, assistant medical officer at the Sanatorium des Pins, arrived at the following conclusions: Tuberculous infection is rare between married persons, even among the working classes, and occurs only after prolonged cohabitation. The incidence of such infection does not exceed 5.2 per cent. in our statistics taken as a whole, and only reaches 11.56 per cent. among cases of open tuberculosis."

E. ARNOULD collected from the literature 48 series of statistics obtained in 9 different countries between the years 1874 and 1924 by 33 observers; among the 53,069 married couples whose cases were recorded he found that tuberculosis had attacked both partners in 4,472 cases.

GEORGES MARTEAU in his inaugural lecture (Lyons, 1925) referred to 24 cases of phthisis affecting both partners, out of a total of 289 married couples. Among 167 families, DENOYELLE found 36 cases of conjugal tuberculosis, out of which infection probably occurred in only 2 or 3 instances, or in about 7 per cent. F. B. HERMANN, in a series of 270 families, found an exogenous origin in only 4.3 per cent. of cases.

H. TECON collected information, from two Lausanne dispensaries, relating to 482 couples among whom husband and wife had shared the same bed, nine times out of ten, during the time when the disease was

¹ "La Tuberculose conjugale, Contagion et Mariage." Paris: Maloine, 1922.

developing. He was able to record 90 cases in which both partners were affected, i.e., 19 per cent. On the other hand, JACOB and PAUNWITZ found both partners affected in only 130 cases out of a series of 1,550 married couples—i.e., 8.6 per cent. of cases. The figures recorded by A. DUFORT are different again: he found both partners involved in 33 cases out of 134 (24 per cent.).

At the Tuberculosis Congress in 1893, EMPIS said that in fifty years of practice he had not witnessed a single case of marital infection if hereditary consumptives were excluded. LEUDET, of Rouen, who has always been recognised as a conscientious clinician, draws the following conclusions, as the result of twenty-five years' experience of practice: among 112 cases where one partner of a married couple was consumptive, he found only 7 cases in which the sound partner became affected, and, in 4 cases out of the 7, the patient was still living at the time when the record was made.

L. ROCHETTE,¹ medical superintendent of the Angeville Sanatorium, quotes in a recent work the results of his inquiries on the subject of infection among a series of 437 tuberculous wives and widows. The proportion of cases (11.2 per cent.) in which husband and wife were both affected corresponds exactly to the percentage given by the law of chance (as will be shown later) when the theory of infection is ruled out of court. ROCHETTE concludes: "It would be some satisfaction to me if I could hope that the existing dread of tuberculosis, under which many patients suffer, would some day give way to a more accurate conception of the dangers of infection—which can only be acquired with any certainty in laboratory experiments."

Clearly, statistics on this question show enormous discrepancies, of which we must seek the explanation.

A. HENRY suggested as an explanation that the

¹ "Tuberculose conjugale et Contagion tuberculeuse." Hauteville: *Lompnes Médical*, t. ii, October, 1930, p. 37.

evidence had been obtained at different times in different countries and from various social classes, including those attending dispensaries, residents in sanatoriums and patients in working-class districts; but his argument scarcely accounts for the range of 2 to 58 per cent. found in the statistics quoted above. Some observers, like JOUSSET and THOM, tried to assess the proportion of cases in which both partners succumbed to the disease—that is to say the incidence of *double mortality*—while most of the others took into consideration all the cases in which both partners were affected simultaneously. Lastly, a few observers, like EMPIS, omit from their statistics all those cases in which the hereditary factor could have played a part. Such statistics depend for their accuracy on the care with which evidence of heredity has been sought.

The important point is that all those who, like myself, have sought systematically for evidence of heredity, have reached the conclusion that infection between married persons does not occur.

During the past thirty years I have studied some thousands of tuberculous patients and hundreds of consumptive families, without detecting a single case in which it could be stated beyond cavil that infection between husband and wife had occurred.

There are millions of tuberculous patients in the world, and if infection occurs between adults there should be thousands of cases on record. I have repeatedly asked medical friends and acquaintances to show me a few thoroughly proven cases of conjugal infection, and I am still waiting for the first example. And thousands of examples would be necessary to warrant the conclusion that infection occurs between adults under ordinary conditions of life.

On the other hand, cases where infection has failed to occur between man and wife, even when they are living under the most insanitary conditions, are innumerable. Among my own acquaintances I can record a striking series of such cases.

I may quote in the first place the case of one of my colleagues, with whom I worked for over a quarter of a century. He suffered from a fibrous form of tuberculosis from which he died twelve years ago; his wife was never affected and is still living. A son of his, who succumbed to generalised tuberculosis a few years before his father's death, left a widow who escaped infection. Another of my colleagues is still in excellent health, though his wife died of tuberculosis twenty years ago. One of my relatives, married to a consumptive now dead, has never suffered from the disease. Another distant relative has always enjoyed excellent health, though his wife died from tuberculosis twenty-three years ago, and his son and granddaughter subsequently acquired the disease. A connection by marriage succumbed to the disease eighteen years ago, but his wife has never shown the slightest symptom of it. A friend of forty years' standing escaped tuberculosis although his wife died of it sixteen years ago; two of their children died at about the age of 20, from tuberculous meningitis.

Among the personnel of my factory I cannot tell how many I have seen fall victims to consumption while their wives remained immune.

I cannot record here all the cases I have personally examined in which infection failed to occur between husband and wife, but a series of 150 cases of the kind seen during the last two years will be found in an appendix at the end of this book. In those cases (19 in all) where both partners were found to be affected I found either a family history of tuberculosis in both partners, or else was unable to obtain sufficient evidence to eliminate the hereditary factor.

In view of these facts I cannot admit that infection occurs between married persons, unless exceptionally.

* * * * *

The question may be examined from another angle, not by trying to determine the incidence of tuberculosis of both partners, but by trying to assess the

proportion of cases in which both partners died of the disease. In the course of some thirty years' work I have been able to collect—from among my immediate acquaintances, the personnel of my factory, the clinical wards of my laboratory, or from hospitals—no less than 322 cases of tuberculosis occurring in both partners of a marriage. Of these, one partner died in 310 cases, and both partners in 12 cases. If we add JOUSSET's series (222 cases, with death of both partners in 9) to THOM's (402 cases, with death of both partners in 25) and mine (310 cases, with death of both partners in 12), we reach a total of 934 cases with death of both partners in 46. According to these figures, in only 5 per cent. of cases can the death of one partner be ascribed to infection acquired from the other; and even this figure is open to question since there is nothing to show that heredity or infection in infancy was not the cause of death. Apart from the possibility of infection between husband and wife there would always be a certain proportion of cases in which both partners died of the disease. The laws of chance furnish reliable evidence on this point.

The Laws of Chance, and Infection in Matrimony.

In drawing conclusions from statistics to support the theory of infection, the part played by coincidence ought to be taken into account. In a previous publication¹, by applying the principles of the laws of chance, I was able to show that infection could not be regarded as the responsible factor in the various cases cited by those who believe cancer to have a parasitic origin. It is of equal interest to study the way in which the incidence of conjugal tuberculosis is affected by the laws of chance.

Let us first consider the relationship between mortality from all causes and mortality from tuberculosis alone. Thanks to the co-operation of

¹ "Le Cancer, maladies des cicatrices." Paris: Masson. 1929, pp. 83-107.

Dr. VIGNE, director of the Lyons Sanitary Bureau, I have been enabled to examine the death certificates issued in this city between the years 1906 and 1925. In the total series of 188,124 deaths occurring during that time, the cause of death was not mentioned in 28,509 cases. The number in which the cause of death had been ascertained was, therefore, 159,615, and among these in 34,474, or 21.59 per cent., death was stated to be due to tuberculosis.

It would be scarcely reasonable to argue from these figures as a whole, since in the vast majority of cases people do not marry before the age of 20. We may therefore eliminate from the series all deaths—whether from tuberculosis or other causes—occurring before that age. Of the 159,615 deaths recorded, the age distribution is as follows: between 0 and 20 years of age, 28,731 deaths; over 20 years of age, 130,884. That is to say, 18 per cent. of deaths occurred in persons under, and 82 per cent. in persons over 20 years of age.

Of the 34,474 deaths from tuberculosis, 7,239 occurred in persons under 20, and 27,235 in persons over 20—or 21 per cent. and 79 per cent. respectively. We need only consider, however, those figures which refer to persons old enough to marry: that is to say 130,884 deaths from all causes and 27,235 deaths from tuberculosis. Deaths from tuberculosis, then, represent approximately 20 per cent. of deaths from all causes. In other words, among the series of deaths occurring after the age of 20, for every person who dies from tuberculosis, 4 die from other causes; or one-fifth of the adult population succumbs to the disease.

Let us take a group of married couples at random: if x represents the average number of those who will die from causes other than tuberculosis, y the number of cases in which one partner will succumb to tuberculosis, and z the number of cases in which both partners will succumb to the disease, we get the following equations:—

$$\begin{aligned} x + y + z &= a \\ 2x + y &= \frac{4}{5} \times 2a \\ y + 2z &= \frac{1}{5} \times 2a \end{aligned} \quad (i)$$

By combining any two of these equations the third can be postulated; in fact the last two equations are based on identical data. The determinant, expressed algebraically, in every case is nil :—

$$\begin{vmatrix} 1 & 1 & 1 \\ 2 & 1 & 0 \\ 0 & 1 & 2 \end{vmatrix} = 0 \left(= 1 \begin{vmatrix} 1 & 0 \\ 1 & 2 \end{vmatrix} - 2 \begin{vmatrix} 1 & 1 \\ 1 & 2 \end{vmatrix} = 1 \times 2 - (2 - 1) \right)$$

For the unknown quantities x and y we get the following values :—

$$\begin{aligned} x &= \frac{3}{5} a + z \\ y &= \frac{2}{5} a + 2z \end{aligned}$$

z can then be given any arbitrary value, either integral or fractional, positive or negative, and values for x and y will then be obtained which will satisfy the equations in series (i) above.

With $z = 1$, we get $x = 61$ and $y = 38$

With $z = 9$, „ „ $x = 69$ and $y = 22$

With $z = 4$, „ „ $x = 64$ and $y = 32$

In the above explanation we have taken x and y as functions of z , but we could equally well have taken y and z as functions of x . The problem, then, cannot be solved by algebra. We must therefore try to solve it by calculating the probabilities.

The problem is of the same type as that which I have previously sought to solve in connection with cancer-haunted houses.¹ It may be expressed as follows: m white balls and b black balls are mixed together, and m balls are then withdrawn at random. What are the chances that the balls withdrawn will comprise: m white balls; $m-1$ white balls and 1 black ball; $m-2$ white balls and 2 black balls; $m-3$ white balls and 3 black balls; . . . and so

¹ AUGUSTE LUMIÈRE and PIERRE LEMAIRE. "Maisons à cancer et calcul des probabilités." *Les Néoplasmes*, Nov.-Dec., 1927, p. 333. Also AUGUSTE LUMIÈRE. "Le Cancer, maladie des cicatrices." Paris: Masson. 1929, p. 83.

on down to m black balls? I will not set out the details of my reasoning here, but will merely give my conclusions; those who are especially interested in the steps of the problem will find them set out fully in my previous work. Suffice it to say, I was able to formulate the following equations:—

$$P_0 = \left(\frac{w}{w+b} \right)^m$$

$$P_1 = P_0 \times \frac{b}{w} \times \frac{m}{1}$$

$$P_2 = P_1 \times \frac{b}{w} \times \frac{m-1}{2}$$

Let us assume that 4,000 white balls were mixed with 1,000 black balls (i.e., a ratio of 1 black ball to 5 of the total number, corresponding to the number of deaths from tuberculosis in proportion to the number of deaths from all causes); and that 2 balls were withdrawn at a time. That is to say:—

$$m = 2 \quad w = 4,000 \quad b = 1,000$$

P_0 stands for the probability, or chance, that the 2 balls withdrawn will both be white; P_1 for the chance that there will be 1 white ball and 1 black ball; and P_2 for the chance that 2 black balls will be withdrawn. If we substitute the values agreed upon for m , b and w into the foregoing equations we get:—

$$P_0 = \left(\frac{4,000}{5,000} \right)^2 = 0.8^2 = 0.64$$

$$P_1 = 0.64 \times \frac{1,000}{4,000} \times \frac{2}{1} = 0.32$$

$$P_2 = 0.32 \times \frac{1,000}{4,000} \times \frac{2-1}{2} = 0.04$$

Out of 100 draws we should therefore expect to find:—

That both balls were white 64 times;
One ball was white and one black 32 times;
Both balls were black 4 times.

These values satisfy the series of equations (i) above,

which I postulated in trying to solve the problem algebraically.

Apart, then, from any question of infection, we should expect to find, in a series of 100 married couples, that 64 would die from causes other than tuberculosis; and that in 32 cases one partner, and in 4 cases both partners, would succumb to the disease.

I have sought experimental confirmation of these mathematical calculations. This can be done quite simply. Let us place in a bag 4,000 white balls and 1,000 black balls, the white balls representing those persons who will die of causes other than tuberculosis and the black balls representing those who will succumb to the disease. Let us mix the balls as thoroughly as possible, and then proceed to draw out 2 balls at a time. Following this method I recorded the result of the draw on 3,000 occasions; the figures are given below:—

Number of times 2 white balls were withdrawn:

$$623 + 660 + 643 = 1926$$

Number of times 1 black and 1 white ball were withdrawn:

$$340 + 300 + 310 = 950$$

Number of times 2 black balls were withdrawn:

$$37 + 40 + 47 = 124$$

The average figures for every hundred draws were:—

2 white balls: 64.2 per cent.

1 white, 1 black ball: 31.66 per cent.

2 black balls: 4.13 per cent.

These figures confirm the accuracy of the previous calculation. They are not identical, however; in practice I obtained 64.2 instead of 64, 31.66 instead of 32, and 4.13 instead of 4. This was due to the fact that the numbers used were too small, the laws of chance becoming more exact in their application as the numbers involved increase in size. If I had gone on withdrawing balls, the theoretical and practical figures would have approximated more and more closely until at last they were identical. Considerable variations in results may be obtained in a restricted

series of draws : for example, in one series of 100 draws I withdrew ten pairs of black balls ; if this

Number of times 2 white balls were withdrawn		Number of times 1 white ball and 1 black ball were withdrawn		Number of times 2 black balls were withdrawn		TOTALS	
77	21	..	2	..	100
68	28	..	4	..	100
66	32	..	2	..	100
62	35	..	3	..	100
66	24	..	10	..	100
68	29	..	3	..	100
64	33	..	3	..	100
63	34	..	3	..	100
68	28	..	4	..	100
58	36	..	6	..	100
<hr/>		<hr/>		<hr/>		<hr/>	
660			300		40		1,000
62	34	..	4	..	100
67	26	..	7	..	100
64	30	..	6	..	100
64	33	..	3	..	100
67	29	..	4	..	100
67	30	..	3	..	100
54	37	..	9	..	100
58	38	..	4	..	100
66	31	..	3	..	100
74	22	..	4	..	100
<hr/>		<hr/>		<hr/>		<hr/>	
643			310		47		1,000
63	34		3		100
61	36	..	3	..	100
67	27	..	6	..	100
67	30	..	3	..	100
67	31	..	2	..	100
60	36	..	4	..	100
61	36	..	3	..	100
59	37	..	4	..	100
60	36	..	4	..	100
58	37	..	5	..	100
<hr/>		<hr/>		<hr/>		<hr/>	
623			340		37		1,000

series had been used as a basis of calculation, the inferences drawn from it would have been erroneous.

On the other hand, in another series of 100 draws pairs of black balls were withdrawn only two or three times, a finding which might have led to exactly opposite conclusions. It is only by taking statistics from several thousand draws that valid conclusions can be reached.

I have formally demonstrated then that, strictly according to the laws of chance operating upon large numbers of cases, and quite apart from any question of infection, in a country where the mortality from tuberculosis is responsible for one-fifth of the total number of deaths, out of every 100 married couples both partners will die from causes other than tuberculosis in 64 cases, one partner will succumb to tuberculosis in 32 cases, and both partners in 4 cases. There will be, therefore, 36 ($32 + 4$) couples out of 100 who will suffer from tuberculosis, and of these, in 4 cases—that is to say in one-ninth, or 11 per cent. of cases—both husband and wife will die of the disease. So that among 100 married couples of whom one partner dies of tuberculosis we should expect to find, on an average, that the second partner succumbs in 11 cases.

Our statistics, however, give us an incidence which falls short of even 5 per cent. This is accounted for by the fact that the figures were compiled prematurely, before the death of the second partners of these marriages. Only couples whose final fate is known should be considered in compiling such statistics.

Let us resume the inquiry which is to furnish the final arguments against the theory of infection between adults. If the incidence of the death of both partners is not in excess of 11 per cent. of the total number of cases in which one partner is affected, or if, out of 100 couples taken at random, we find not more than 4 cases in which both partners succumbed to tuberculosis, we shall be able to assert that conjugal infection does not occur. And in point of fact these figures are not exceeded.

*Transmission of Tuberculosis as a Result of Cohabitation,
or Protracted and Frequent Contacts with Patients
offering Open Lesions.*

In his "Pathologie Interne," J. FRANCK wrote :
"When we consider that doctors often associate with thousands of consumptives without taking any precautions, that in hospitals nurses attend on consumptives day and night without showing a greater tendency to suffer from diseases of the lungs than other people, does it not become strikingly apparent that the disease is not infectious?"

Statistics of the mortality among the staffs of sanatoriums and hospitals for tuberculous patients always tend to bear out the contention that the disease is not infectious among adults. At the Congress in 1888, FERRAND stated that no case of infection had been registered for ten years at the Argeles Sanatorium.

In the 1890 issue of *Le Progres Medical*, the report of Dr. HOPT DE SODEN's observations ended with the words : "These observations, it must be admitted, are contrary to the theory that consumption is infectious." In this locality, where large numbers of consumptives used to come to spend part of the year, keepers of lodging-houses, servants and attendants, over a period of thirty-four years, did not contribute a greater proportion of victims to the disease than the rest of the population. At Falkenstein, Goebersdorf and Davos the same findings have been recorded. The climate of Madeira has attracted large numbers of consumptives for the past century, but, according to LANGERHAUS, the disease rarely affects those without a family history of tuberculosis.

The foregoing facts are recorded in Dr. JOUSSET's work, and the following arguments are quoted from the same source.

"We find in Dr. LAUTH's book on the treatment of tuberculosis at high altitudes the following passage, demonstrating once again the fact that infection

from man to man does not occur : ' I know a village situated at an altitnde of 1,300 metres (4,264 feet),' this author writes, ' which has been frequented by consumptives for at least ten years. During the winter the inhabitants all lead the most unhygienic life imaginable, crowded into rough chalets, the openings of which scarcely let in air or light. So far not a single one of the inhabitants has become consumptive, though the patients who come to stay there during the winter take no precautions with regard to their sputum, and spittoons and sputum cups are undreamt of.'

" Could there be any more striking demonstration that tuberculosis is not infectious ? " asks JOUSSET ; " and what a reflection it is on the value of compulsory spittoons ! And yet the writer believes in the theory of infection, for he adds : ' Obviously, however, a day will come when cases of infection will arise.' "

And JOUSSET makes the following remark after quoting the last phrase :—

" *Obviously* is delightful ; the adverb does away with any need for proof. But if Dr. LAUTH will allow me to indulge in prophecy, that event will take place on the day that one of these consumptives propagates his species and his ailment together, with one of the village women as his accessory during the fact."¹

THOMAS WILLIAMS' statistics, collected from the Brompton Hospital, are no less convincing.² Over a period of thirty-seven years, 13,262 cases were admitted to this hospital, three-quarters of which were cases of consumption. Out of 341 medical attendants and nurses only 15 became tuberculous—i.e., 4.39 per cent.—a proportion which certainly does not exceed the average incidence among the community outside the hospital. In this hospital, at that time, cases of tuberculosis were not segregated, and sputum cups were never disinfected.

¹ P. JOUSSET. " Prophylaxie de la Tuberculose," p. 86. Paris : Baillière et Fils. 1907.

² *The Practitioner*. June, 1898.

At one time rumour ascribed an unduly high mortality from tuberculosis to army nurses, and this misconception led Surgeon-General KELSCH to submit a protest to the Academy of Medicine ; in support of this protest he quoted official statistics showing that the incidence of tuberculosis was at that time 5.61 per 1,000 for male nurses, whereas it was 8.72 per 1,000 among the infantry.

Among 108 nurses in the Friedrichain Hospital, 3 were found to be tuberculous, according to FURBRINGER ; one had shown definite signs of the disease before entering the institution, and another had a family history of tuberculosis. At a session of the Berlin Medical Society held in 1899, the same writer showed that in a series of statistics which he had drawn up, out of 708 nuns only 13 became consumptive ; in 6 of these cases the disease had been present before they undertook hospital service, and in 6 others there was a family history of tuberculosis. It may be noted that his figures are anomalous, the incidence of the disease being far below the figure recorded for the community at large. Even if some errors have crept into the compilation of these records, they unquestionably tend to disprove the theory of infection, at any rate during middle age. The same holds good of PIDOUX's observations ; out of 5,000 cases he found only 4 in which infection might have been responsible for the disease. BAEHMER assures us that at the Goebersdorf station, through which 12,000 consumptives have passed, the mortality rate has decreased among the native staff.

While the foregoing information, though somewhat antiquated, may reasonably be relied upon, it would be hazardous to take corresponding contemporary statistics into account, since certain sanatoriums have drawn upon tuberculous patients for their staff. A practitioner suffering from tuberculosis, with a family to support, will try to obtain a sanatorium appointment, where, while carrying on his profession, he will benefit by climatic treatment. The same is

true of male and female nurses and of house physicians. Care must be taken not to class these subjects as infected cases.

Moreover, account should be taken of the fact that in certain localities, such as Hauteville, a number of tradespeople and workmen who have suffered from the disease have settled in the neighbourhood after undergoing sanatorium treatment. Little attention has been paid to this point, for, ever since it has been accepted that infection is the only factor to be considered in the transmission of tuberculosis, demographic investigations have been entirely neglected. What would be the good of undertaking them since the problem is finally solved! Dogma has killed scientific research, and thought has become subservient to routine.

And yet GUILLEMIN wrote in 1912: "Satisfied that tuberculosis is not infectious, I never segregated any of the consumptives from the asylum of the Freres de Saint Jean de Dieu. There they are, 450 of them, oozing tuberculosis, so to speak, at every joint; and for the last twenty-five years, during which the records have been strictly kept, and for the last ten years during which I have kept records of my own observations, not a single case of infection has been detected."¹ WILLIAMS noted in the *British Medical Journal* that he found only 2 or 3 cases of infection among 337 male nurses.

In 1925 Martin KIRCHNER, investigating the question of risk to medical practitioners, published a paper based on statistics drawn from 549 public or private institutions: hospitals, clinics and sanatoriums. He tried to determine what proportion of the medical and nursing staff were actually infected by patients.²

According to him the incidence of infection

¹ GUILLEMIN. "La Tuberculose n'est pas une maladie contagieuse." Paris: P. S. Jouve and Co., 1922.

² MARTIN KIRCHNER. "Contagion de la Tuberculose parmi le personnel médical et infirmier." *Zeitschr. für Tuberculose*, t. xliii, 1925, No. 5, Oct.

among the medical and nursing staffs together was as follows:—

1.36 per cent. in general hospitals.

2.42 per cent. in university clinics.

1.89 per cent. in private sanatoriums.

Among the nursing staff the incidence was 1.44 per cent. and the medical practitioners infected accounted for only 0.77 per cent. of the whole.

Martin KIRCHNER suggests that the Government should keep a record of all cases of infection, which, he says, are after all very rare, and need give rise to no apprehension among those who attend consumptives.

“It seems,” he writes, “that infection is exceptional in institutions furnished with modern equipment.”

He will allow me to point out, in addition, that infection, exceptional in institutions where sanitary principles are duly observed, was no commoner, according to other writers, in the old hospitals where no particular precautions were taken; and furthermore that it ought to be demonstrated, in the few cases attributed to infection, that heredity or an inherited tendency to the disease has not played some part in its development. No proof of this is offered by those statisticians who have dealt with the problem of transmission through infection.

I have, for my part, undertaken inquiries at some of the climatic stations where consumptives are received. Dr. JAQUEROD, chief medical adviser at the Grand Hotel de Leysin Sanatorium, said that for the last thirty years he has never seen a single case of infection among the staff of the institution. The managing director of the station informed me that no case of infection has been recorded among the nursing staff, the hotel staff or the laundry staff, though the personnel of these services are always recruited from among people who are free from the disease. As for the general population of the place, the death-rate from tuberculosis is noticeably

lower among them than among the inhabitants of other towns in the same country.

As director of the Felix MANGINI Sanatorium in Hauteville from its foundation—that is to say for about thirty years—I have had every chance to collect information about cases of infection, the more so since the medical staff have always given me their courteous co-operation. Since this sanatorium was opened the staff, comprising nuns, male nurses and various operatives, has numbered about 500. During that period only 3 cases of tuberculosis among the staff have been recorded.

(a) The first was a nun who arrived in good health, and remained four years, when she developed a progressive lesion. She returned to her convent where she shortly afterwards died. It is not known whether there was tuberculosis in her family.

(b) The second was an employee, a Hauteville man, who was found physically unfit for military service in 1910, on account of chronic bronchitis. Nevertheless he was engaged to work at the sanatorium in 1912 when his health was perfectly sound. He was called up in 1914 and remained at the front throughout the war without developing any chest trouble. Having resumed his employment at the sanatorium in 1919, he was laid up a year later with a grave attack of sero-fibrinous pleurisy, from which he made a complete recovery.

(c) Lastly, a joiner at the sanatorium scratched his right forefinger one day on a nail embedded in an old board. Six months later he had caries of the bone, then arthritis of the elbow, and ultimately signs of pulmonary tuberculosis. The man left the sanatorium, but lived for five more years in the neighbourhood and then died.

Admitting that infection became generalised in the last case, and that it was a direct consequence of the wound, it is obvious that the case was one not of infection but inoculation. As a matter of fact, however, there is no proof that the wound was the

sole cause, for in most accidents of this kind, where anatomical tuberculosis is shown to be present, the lesion heals without leaving a trace unless the subject is hereditarily predisposed to the disease.

However that may be, only one of these three cases can be accepted as due to infection—that of the nun ; and even this is doubtful, the part possibly played by heredity not having been taken into account.

On the other hand, it has been possible to observe, in the same institution, facts which point to the opposite conclusion. For example, two nuns were sent to the sanatorium from their convent showing signs of fibrous tuberculosis. One of them has just died after twenty-two years' service, and the other is still looking after consumptives, as she has done for the last thirty years, without showing any signs of progressive disease.

Another case is also very striking : that of a man who has had charge of the patients' soiled linen for the last thirty years. Despite repeated warnings and recommendations he takes no precautions, and will frequently take his midday nap in the laundry upon heaps of unwashed linen. His attention has been called to the risks of infection in vain ; he listens to remarks of the kind with a grin, and it must be admitted that his carelessness does not seem to have proved disastrous. He has now been working in his own way for over a quarter of a century, and his health has always remained excellent.

* * * * *

Let us consider a group of people at work for thirty years in any healthy occupation, and let us suppose that during that time 500 have been employed. The incidence of tuberculosis among them in that period is likely to amount to some dozens of cases. How is it that, during a similar period, in an environment as heavily infected as a sanatorium, an equal number of workers, in close contact with hundreds of patients coughing up tubercle bacilli, have only included

three cases of tuberculosis. This is surely curious, and one is tempted to draw the paradoxical inference that in order to escape tuberculosis the best plan is to associate with consumptives !

I once asked a medical friend, imbued with faith in the theory of infection, to account for this puzzling state of affairs.

"Why, it's allergy," he cried. "Any person receiving a dose of tubercle bacilli acquires a certain power of resistance."

"Since self-vaccination is so efficient," I replied, "tuberculosis must be regarded as scarcely infectious at all in practice ?"

"Don't you believe it !" he said. "With subjects who have not previously encountered the disease the great danger is one of massive primary infection ; and with subjects who have previously received small doses there is always a danger of reinfection."

"Very well," I replied. "But, seeing that no one is more exposed to massive primary infection or reinfection than those who live in constant contact with consumptives—that is to say doctors, nurses, and so on—please explain why the personnel of this sanatorium escape the disease."

No answer was vouchsafed.

How, then, can we account for this peculiar immunity ? Three hypotheses occur to me.

(1) We may have dropped by chance upon a specially favourable series ; but this is scarcely admissible, since the low incidence of tuberculosis among the staff is comparable with that recorded in other hospitals and sanatoriums.

(2) The sanatorium staff, living in a locality specially suited to the prevention of tuberculosis, benefits by being in the best conditions to resist infection.

(3) These members of the staff, by absorbing continually a very small quantity of tubercle bacilli, may acquire an immunity which protects them against invasion by more massive doses of bacilli, or against activation of the virus with which they

have previously become impregnated, either by inheritance or accidentally.

An explanation might perhaps be forthcoming from the experiments of KRAUSE and STUART-WILLIS who investigated the influence of reinfections on allergy and immunity in tuberculosis.¹ Having inoculated an animal on successive occasions with strains of tubercle bacilli of varying virulence, they found that primary immunity, conferred by a suitable dose, might constitute a remarkably efficient defence ; but that allergy is decreased by repeated reinoculations of a moderately virulent bacillus at short intervals.

Other things being equal, the resistance of the subject is lessened more by a large than by a small second dose. When adequate dosage is reached the animals treated show a condition of chronic intoxication, and their immunity can be lowered to such a degree that inoculation with a given dose of bacilli may produce more serious lesions than would be produced by the same dose in subjects which had never been immunised.

If reinfection can cause the disappearance of the allergic state, even leading at times to a condition of hypersensitiveness, the supposed immunity of the personnel of sanatoriums becomes inexplicable. The experiments of KRAUSE and STUART-WILLIS, however, were made under conditions essentially different from those experienced by attendants in contact with tuberculous patients. Whatever hypothesis is put forward to explain the facts, it appears clear, in my view, that infection does not occur between adults under the conditions of ordinary life, even when such adults live among consumptives.

* * * * *

So far I have considered only the theory of conjugal infection, and of the transmission of tuberculosis as

¹ ALLEN K. KRAUSE and H. STUART WILLIS. *The American Review of Tuberculosis*, t. xiv, No. 3, 1926, pp. 316-343.

a result of cohabitation or prolonged contact with tuberculous patients, but before bringing this discussion to a close I must quote two examples which have been given as instances of infection. These examples were recorded by VIALETTE and have been quoted by MUSGRAVE-CLAY, DEBOVE and others.

Jean A., the son of consumptive parents, married Antoinette A., the child of healthy parents. Jean A. shortly developed signs of tuberculosis and died; his widow married again and then died of tuberculosis, after transmitting the disease to her second husband. But the disaster did not end there; during the last months of her illness Antoinette had been attended by her niece, Marguerite M.—wife of Joseph B.—who was free from tuberculosis, and the child of healthy parents. Marguerite M. died of tuberculosis in her turn, after transmitting the disease to her husband, who also succumbed to it.

In making the statement that the parents of Antoinette A. and Joseph B. were free from tuberculosis the observers were probably contented with the assertions of the persons in question, or of their families. Most likely the parents were never examined by a medical practitioner, and certainly they were not examined radioscopically since this method of investigation did not exist at the time; it is even possible that one or several of them were dead at the time when the interrogation was carried out, and that the more or less accurate memory of the patients was relied upon. With such methods, the absence of the hereditary factor cannot be regarded as proven. Series of this kind appear to be extremely rare, and a search through medical literature will reveal hardly any comparable examples. Yet the laws of chance, quite apart from infection, should furnish us with a few analogous cases.

Actually, given one consumptive, there is, in my own district, one chance in five, on an average, that his immediate associate, whether a relative of his or not, will one day succumb to tuberculosis. The

odds that his four nearest associates will fall victims to the disease are :—

$$\frac{1}{5 \times 5 \times 5 \times 5} = \frac{1}{5^4} = \frac{1}{625}$$

So that, on an average, out of 625 consumptives there will always be one whose four nearest associates succumb to tuberculosis, quite apart from any question of infection. If this proportion were to be exceeded we could say that tuberculosis was infectious, but if it is not exceeded I can leave the reader to draw his own conclusions. And in point of fact, of course, it is not exceeded; for one has to take an enormous amount of trouble to find a complete series of the kind among the thousands of patients one encounters.

I have checked the figure given above experimentally. Out of a bag containing 4,000 white balls and 1,000 black balls, I withdrew balls in groups of 4. The results of the draw are set out in the following table :—

NUMBER OF DRAWS.

4 white	3 white 1 black	1 white 3 black	2 white 2 black	4 black	TOTALS
416 ..	421 ..	136 ..	25 ..	2 ..	1,000
410 ..	401 ..	165 ..	23 ..	1 ..	1,000
397 ..	420 ..	144 ..	39 ..	0 ..	1,000
400 ..	402 ..	155 ..	41 ..	2 ..	1,000
378 ..	405 ..	172 ..	42 ..	3 ..	1,000
2,001	2,049	772	170	8	5,000

Out of 5,000 draws, 4 black balls were withdrawn on 8 occasions, which corresponds to one draw of 4 black balls out of 625 : that is to say, exactly the figure obtained by calculation. Probably another series of draws would not give the same exact result, but would give figures above or below the average; but with increasing numbers of draws these variations would tend to compensate each other, and we should ultimately obtain the same percentage as is obtained by calculation.

Cases similar to that of Antoinette A. will therefore

occur from time to time, purely as the result of chance, and without infection playing any part in their production.

* * * * *

Cases of pseudo-infection as a result of cohabitation were considered to be rare at the end of the last century, since the Berlin Medical Society, in an investigation into this question in 1884, was able to collect only 46 examples in support of the theory of infection, and of these 6 had to be rejected. In the face of these discouraging results supporters of the theory of infection attempted to prove their case by other methods; following the plan of Dr. JOUSSET they instigated inquiries among medical practitioners, collecting their opinions on the ætiology of tuberculosis.

(a) In 1873, BOWDICH made such an inquiry among 210 fellow-practitioners in Massachusetts, and obtained the following replies :—

110 practitioners believed infection to occur.
45 denied its occurrence.
27 were doubtful.
28 failed to reply.

(b) The *Collective Investigation Committee* arranged a similar inquiry among members of their association; 1,078 replies were received, of which only 261 supported the theory of infection and 39 were doubtful.

(c) The *Societe Medicale des Hopitaux de Paris* asked members for an opinion on the same subject in December, 1884 (VALLIN's report).

83 replies were received from practitioners.
57 believed infection to occur.
13 denied its occurrence.
13 were doubtful.

VALLIN's report emphasised the fact that infection was transmitted most frequently from husband to wife, less commonly from wife to husband, still less commonly between brother and sister, and least commonly of all between more remote relations, including

cousins, uncles, nephews and brothers-in-law. *The danger of infection decreased as the relationship became more remote.*

How can this conclusion be reconciled with the theory of infection? If infection is responsible, relationship should not affect the figures; it is the degree of exposure which counts. VALLIN goes so far as to concede that the hereditary factor may mask infection or augment it. All this is rather unscientific and does not prove much.

The unreliability of inquiries into family history, the discrepancies of opinion, the variations found in different countries and at different periods give an impression of inconsistency on this point which is far from convincing.

CHAPTER III.

DISCUSSION OF CLINICAL ARGUMENTS IN FAVOUR OF THE THEORY OF INFECTION.

IF tuberculosis were infectious, infection should occur more frequently among those who live in contact with consumptives than among those who seldom encounter them. It stands to reason that if persons living in a tuberculous environment do not become infected, tuberculosis is not infectious. In actual fact such persons do not become infected; medical attendants invariably escape the disease, and I have still to learn of a *single instance* in which a medical man who does not come of tuberculous stock has been infected by his patients. Perhaps this rare bird has not been sought very zealously, but in any case he has not been produced. I cannot help feeling, however, that supporters of the theory of infection would not have failed to quote such a telling argument had it been available. And in any case a large number of examples would have to be found in order to warrant the view that tuberculosis is infectious.

What are the objections raised to these conclusive facts? Clinical objections to them fall into three groups.

(1) Apparent infection is said to occur in adults, where observation has been superficial and no investigation has been made into the patient's heredity.

(2) Arguments are put forward based on allergy and skin reactions.

(3) Conclusions are drawn from the occurrence of tuberculosis in negroes.

Apparent Infection occurring in Adults.

A typical example of this kind has been widely quoted, and was apparently so sound that a scientist who writes under the pen-name of "Hippocrate" allowed himself to be misled, and actually quotes this example in a review of my book which appeared in *Le Progres*, the Lyons daily newspaper.

Some twenty medical students, it was stated, who had frequented the tuberculosis wards of the Lyons hospitals, fell victims to the disease a few years ago. As the exact number said to have acquired the disease was not given I took the trouble to find it out ; one of the hospital surgeons estimated the number of young men affected at sixteen. I asked to be allowed to see the records of these cases in order to study them in more detail. I found that no records of observations on individual cases had been kept, and that the information had been furnished from memory without any supporting evidence. Among those who were collaborating with me in my work were a certain number of house-surgeons at various Lyons hospitals ; I asked one of them to make as detailed an inquiry as possible into these cases of alleged infection. In spite of thorough research, undertaken with the help of his colleagues in other hospitals, this young man was able to obtain evidence of only 9 cases of students who had shown tuberculosis in 1928, and an undoubted family history of tuberculosis was recorded in the case of 5 of them. No details are available concerning the family history of the remaining 4 ; possibly no inquiries were made on this point in some cases. On the other hand, since there has been no opportunity to question these patients or to examine their parents, the part played by heredity cannot be estimated.

Let me add that tuberculosis wreaks its worst havoc among young people round the age of 25, that students are often overworked, and that consequently it is not surprising if, among this class of subjects, hereditary tendencies or lesions show themselves for the first

time during the period of medical training. The incidence of tuberculosis among the seven hundred odd medical students in Lyons is by no means excessive, especially if the laws of chance, which explain the unequal distribution of cases over a series of years, are taken into account.

Again, why should 1928 be the only year to be considered? Was not tuberculosis equally infectious during the preceding years? Passed on from one person to another, and being exaggerated in transit, this rumour, depending on a few coincidences, created a lively impression in the minds of the Lyons hospital community.

What evidence is there in support of the theory of infection between man and man? Arguments analogous to the last—which I should be more inclined to call fables. “It is the consumptive who is not sufficiently ill to be an invalid,” “Hippocrate” states, “who spreads tuberculous meningitis; it is the professor, affected with the disease and unaware of it, poor fellow, who is responsible for the appearance of two or three cases of meningitis among his students; the employee and the servant cause similar tragedies. . . .” And more to the same effect.

When more exact information with regard to the facts is demanded, none appears to be available. Not a single case has been the subject of thorough, methodical investigation, no one has considered whether any cause other than infection can be implicated, and the parents of the patients have never been given adequate examination.

Considering the enormous numbers of persons affected with tuberculosis, frequent coincidences must occur and give rise to faulty conclusions. It is solely on such coincidences that the theory of infection has been based.

If the son of a tuberculous parent has been in contact with another consumptive patient and subsequently shows signs of the disease, infection will be accepted as the explanation without further question; but I have heard of a case in which, in spite of the most

elaborate precautions being taken to protect the two children of a consumptive from infection, both succumbed to the disease.

If two cases of meningitis arise, as recently happened, in a school class under the charge of a consumptive teacher, the teacher is immediately accused of having infected his pupils ; but no mention is made of the fact that the mother of one of the children died from tuberculosis at the age of 33, or that two brothers of the other child had died in infancy from tuberculous meningitis, before meeting the schoolmaster in question.

Coincidences of this kind make a deep impression on the mind, and lead us to seek the simplest explanation—the explanation which, *a priori*, satisfies our desire to find a scapegoat when we are visited with misfortune, regardless of whether we are venting our rancour upon a person or upon some concrete fact. There are, I repeat, millions of consumptives in the world, and if tuberculosis was infectious, examples of infection would be found *by the thousand*. But, so far, medical literature has contained no report of a single case of infection which cannot be challenged, or a single example, supported by a complete clinical and radiographical investigation of the parents, proving the total absence of the hereditary factor.

The conventional theory exerts such a fascination on most minds that the circumstantial and critical study of various phenomena has been neglected, and the particulars of cases laid before us are therefore often meagre. How can infection, since it does not occur between adults in a tuberculous environment such as a sanatorium, be shown to exist ? How can the evidence be distorted so far that it contradicts the facts ?

The method employed consists in trying to prove that if tuberculosis is not infectious in practice it must be so in theory. In support of this, the allergic reactions to tuberculin, and the development of

tuberculosis among negroes are quoted ; then experiments on animals are tried, and are later extended to human subjects.

Arguments based on Allergy and Skin Reactions.

An allergic state, in theory, would oppose infection to some extent, and would account for the resistance of some subjects, and the susceptibility of others, to infection. In short, allergy would appear to be both a protective and a harmful mechanism ! Let us try to discuss this discrepancy.

(a) *The Allergic Reaction as an Immunising and a Predisposing Factor in Tuberculosis.*—The conventional theory of allergy in tuberculosis is a complete muddle. Several writers, HERVOUET¹ among them, have shown that the explanation offered cannot be reconciled with the facts, and I should not return to this problem if I did not hope to offer a hypothesis which covers the phenomena of the tuberculin reaction—the test which indicates this enigmatic condition of allergy.

Let me, in the first place, recall the fact that VON PIRQUET coined the word “allergy” to denote sensitiveness to tuberculin, considered as a sign of tuberculous infection ; the term soon assumed a wider and more complex meaning when it was found that, in certain cases, a small dose had an immunising effect, and was accompanied by a positive tuberculin reaction. The idea of allergy as a *beneficent force* was naturally accepted at that time among authorities on tuberculosis.

RIST wrote : “ A person who has a negative skin reaction (anergy) is more liable to become tuberculous than a healthy person who has a positive skin reaction (allergy).”

And in another place he says : “ Chance infection with small doses of tubercle bacilli protects and immunises ; to avoid it is neither possible nor desirable.”²

¹ D. HERVOUET. “La Théorie allergique devant la Statistique.” *Le Concours Médical*, 1930, p. 461.

² RIST. “La Tuberculose,” pp. 196 and 287.

It is only right to point out, however, that the allergic state does not prevent the progress of the lesions in confirmed cases of tuberculosis, whether the case is one of experimental infection or one of the types of human tuberculosis seen clinically. On the contrary, in these latter cases, the existence of allergy, it is generally admitted, favours the development of the lesion, so that the same reaction is considered both to offer immunity and to predispose to the disease ! It is just like saying that an object is both white and black, hot and cold, sour and sweet.

According to the conventional theory babies born free from tuberculosis would be infected by the bacillus after birth ; as a matter of fact, the mortality from tuberculosis is comparatively high during the early months of life, but from two years onwards decreases considerably and remains low for a good many years ; during this early period of life the more the occasions of infection are multiplied the fewer the chances that the infant will fall victim to the disease.

This early immunity has been accounted for by the allergic state ; we are asked to believe that a primary infection confers sufficient immunity to render the infant comparatively resistant to tuberculosis. The reaction to tuberculin, which is the test of such immunity, becomes positive. This condition persists without much change during the greater part of youth, and then at the end of adolescence the resistance presumably weakens, and disappears until, at about the age of 25 in women and 30 in men, susceptibility to the disease is at a maximum. Now, during the long period from birth to manhood, the incidence of a positive tuberculin reaction steadily increases, so that at the period when allergy has reached its maximum the odds in favour of a person succumbing to tuberculosis are greatest. The incidence of the disease then decreases with age, while the incidence of positive skin reactions remains as high as ever.

The upshot is that the curve showing susceptibility

to infection at different ages (fig. 3) is found to bear no relation to the allergy curve over a corresponding period (fig. 4). The two diagrams are completely divergent. What explanation is offered of the fact that the allergic immunity, due to a primary infection, declines steadily from the fifteenth to the twenty-fifth or thirtieth year? It has been alleged that the loss

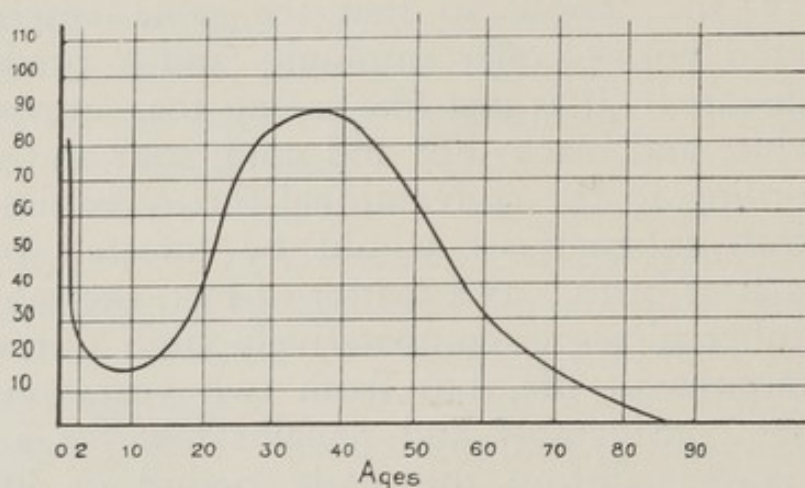
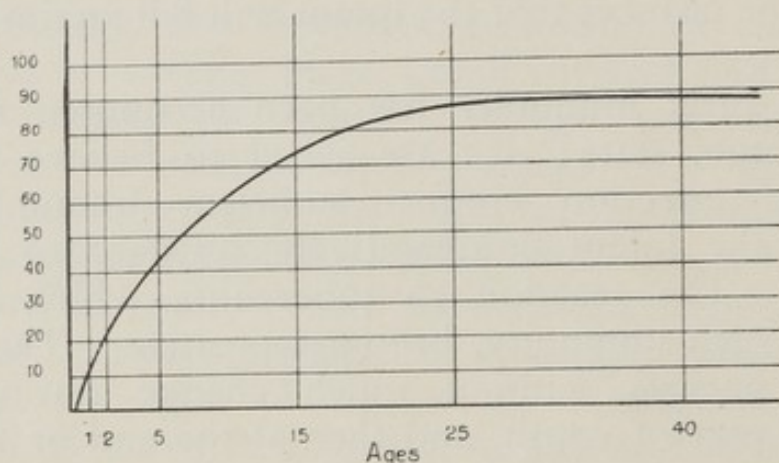


FIG. 3.—The incidence of tuberculosis at different ages.



Percentage of positive skin reactions. Taken from the data of Raymond Letulle and Grisez.

FIG. 4.—Incidence of the allergic reaction at different ages.

of immunity is due to reinfection ; but this is a view with which I cannot agree, for the following reasons :—

In the first place, an infant left in the care of tuberculous parents has innumerable opportunities of being infected and reinfected, since the period of contact is prolonged. A child who lives, for the first four or five years of his life, in a hovel, with a mother who coughs up tubercle bacilli and takes no sanitary

precautions, is exposed to successive chances of infection, the total number of which will multiply as he advances in age.

But, inversely, the curve of mortality after the second year of life falls rapidly. Reinfection, at this stage, then, has no effect. Later on it is equally inoperative; persons married to consumptives, who run the risk of being infected at any moment, ought to be exposed to reinfection more frequently than anyone else; but searching inquiries have shown that transmission of the disease between married persons does not occur. The incidence of tuberculosis is no greater among the married partners of consumptives than among bachelors and spinsters.

The same is true of medical authorities on tuberculosis, who, unless they come of tuberculous stock, are never infected by their patients. I am still awaiting evidence to the contrary. No one runs greater risk of repeated reinfections than the groups of people I have just referred to, namely: children of tuberculous parents living with their family, the husbands or wives of consumptives, and the consultants and staff at sanatoriums. Yet in none of these groups is there any evidence that repeated infections have the slightest influence, although persons in these groups are unavoidably exposed to reinfection.

Per contra, tuberculosis sometimes develops in children of consumptive parents simply because of their heredity; this occurs even when they have been placed in the best possible environment not only to escape repeated infection, but to avoid coming into contact with any infective focus of the disease.

With either class of case the skin reaction is usually positive, whether the patient comes of tuberculous stock, and is suffering from active lesions, or whether he is the child of healthy parents and is himself clinically and radiologically free from the disease and has never shown any sign of tuberculosis, however trifling.

The marked variations in the mortality rate from tuberculosis at different ages (fig. 3) cannot, therefore,

be accounted for by allergy or by repeated reinfections, which are clearly ineffective, if indeed they occur at all. I have long wondered why the allergic reaction should be regarded as a sign of immunity in some subjects, while in others it is supposed to indicate a predisposition to the disease. I saw through the paradox claiming two antagonistic properties for the tuberculin reaction as soon as I realised that confusion had arisen between allergy and infection.

(b) *Allergy without Infection*.—We are told that a benign infection is revealed by a positive skin reaction ; this is perfectly true, but the converse does not hold ; that is to say, a positive tuberculin reaction is not necessarily a sure sign of a benign infection. In a considerable number of cases the reaction is simply a humoral manifestation of a somewhat peculiar specific anaphylactic type. The chief evidence of this lies in the fact that the allergic state can be produced with dead organisms, which are incapable of causing infection. With subjects who have no tuberculous heredity, and who have not been infected immediately after birth, it seems to be possible to produce this humoral state in several different ways.

When we consider that the tubercle bacillus loses its vitality rapidly on desiccation of the sputum, or by exposure of the sputum to light, we may conclude that the non-virulent organisms are in an immense majority in the air. These dead organisms, entering the body chiefly by way of the digestive tract, constitute the antigens which are responsible for the production of the allergic state, just as they produce it in experimental inoculation.

On the other hand, it has been shown that Koch's bacilli are killed by the digestive juices, and micro-organisms exposed to such treatment would consequently be incapable of causing infection.

But, apart from the action of the digestive juices, the body defends itself better than is usually supposed against infection by the living and virulent germ ;

except in massive dosage, it destroys the bacilli, and we have abundant evidence of this fact.

I am referring to the frequency with which accidental inoculation with the tubercle bacillus is followed by cure. This is not merely a question of infection, but of positive inoculation, which is always far more serious and certain than infection.

MAISONNEUVE and VERNEUIL, the eminent surgeons, while making post-mortem examinations on tuberculous patients, both injured themselves and developed, at the site of the prick, a typical tubercle which took about a year to heal. Neither of them had become tuberculous thirty-eight years afterwards.

TORKOMIAN, CHAUVEAU and others were victims of similar accidents, but showed no signs of infection many years after the local lesions had healed. BARTHELEMY, who investigated this point carefully, did not hesitate, at the Tuberculosis Congress of 1888, to declare : "I can say that I have never seen a single case of generalised or visceral tuberculosis following a local tubercle produced by accidental inoculation, whether it was left untreated or treated surgically."

Certainly some rare cases are quoted where generalised spread seems to have occurred years after healing of the local inoculation, but they invariably refer to persons who come of tuberculous stock.

LAENNEC died of consumption at the age of 45, twenty years after acquiring a local tubercle as the result of an infected prick. He was six years old when his mother died of phthisis. It would be unjustifiable to conclude that his terminal illness was due to the tubercle accidentally acquired twenty years before, rather than to heredity.

Be this as it may, there can be no doubt that a positive tuberculin reaction is frequently found in persons who have never had the disease ; or at all events if they have at any time developed tuberculous lesions, they have overcome the invading organisms, and can no longer be regarded as carriers of the disease. The allergic reaction is an indication of

the capacity of the organism to resist fresh onslaughts of the bacillus. It is unquestionably an immunity reaction.

(c) *Allergy in Infected Cases.*—It cannot be denied that patients with bacillary lesions, whether latent or obvious—that is to say, patients who are carriers of the living organism—also react to tuberculin. Children of tuberculous parents at birth may already be impregnated with the filtrable virus of the bacillus or with the organisms themselves in a saprophytic form, the presence of which may not be suspected until long afterwards (not, as a rule, until about twenty years have elapsed), when they become pathogenic; in the same way, infants vaccinated with B.C.G., or animals inoculated with the filtrable virus, will show a positive tuberculin reaction, which may, however, only develop some time afterwards.

In all consumptives the disease shows a series of successive exacerbations which are characteristic of tuberculosis. In my opinion allergy has nothing to do with these exacerbations, which appear, not as a result of the allergic condition, *but in spite of it*. Allergy is never a predisposing cause; but, in tuberculous persons, it is one of the signs of the disease, one of the characteristics of which is to show successive exacerbations. It is because allergy has been confounded with infection that totally irreconcilable properties have been ascribed to it.

Allergy is neither more nor less than an indication of immunity which manifests itself just as well in consumptive patients as in persons whose systems are free from the tubercle bacillus, but who are in an anaphylactic state.

Immunity.

In an admirable report on allergy, read before the Tuberculosis Congress at Lyons in 1928, Prof. P. COURMONT pointed out the difference which he had observed between allergic and anaphylactic phenomena. He took as the basis of his argument the facts

that: tuberculin does not sensitise the subjects into whom it is injected, or only sensitises them with difficulty; that a second injection of tuberculin into allergic subjects does not affect the type of reaction; and that though a rise of temperature is one of the characteristic features following such inoculation, there is no similar rise following sensitisation with common proteins. Arguing from these data he questioned the anaphylactic character of allergy.

I think his contention open to question for the following reasons: In the first place, tuberculin is a very different thing from a culture of Koch's bacilli; the proteins have been modified by heat in the presence of foreign substances, notably glycerine. Furthermore, let me recall the main principle of anaphylaxis, as I have summed it up: When a foreign protein is introduced into the system of an animal the body fluids produce a specific antibody which precipitates the antigen.

It is precisely this which takes place in Koch's phenomenon. Following a preliminary inoculation with bacillary proteins (prepared from bacilli which are dead and therefore incapable of producing the disease), a second inoculation with the same protein cannot be tolerated. This is an anaphylactic phenomenon complicated by the fact that the precipitated antigen—precipitated by the antibodies in the tissue fluids of the sensitised subject—cannot be absorbed by the tissues but has to be excreted in some way. The symptoms produced may vary, just as the symptoms vary which are produced by the intravenous injection of certain synthetic colloidal metals, being sometimes associated with hyperpyrexia and sometimes with a subnormal temperature.

The characteristic features of *tuberculous anaphylaxis* very likely depend on the properties of the precipitate formed. But the phenomenon is certainly anaphylactic in nature, because the protein obtained from cultured tubercle bacilli is a powerful antigen, capable of producing a high degree of intolerance to a second

inoculation, in a subject who has received a primary inoculation.

This type of immunity, dependent on allergy, explains the results of a suggestive experiment made by F. BEZANÇON and BRAUN; these observers, by the insufflation of 1 to 2 mgm. of human tubercle bacilli into the trachea of a guinea-pig, were able to produce tuberculous bronchopneumonia which led to rapid caseation. The organisms, multiplying rapidly in the alveoli, produced lesions identical with those of caseous tuberculous bronchopneumonia. BEZANÇON and SERBONNES showed that when the experiment was repeated with guinea-pigs which had received a subcutaneous injection of virulent bacilli a few weeks before, the lesions produced by intra-tracheal insufflation of bacilli were entirely different. Following the insufflation, on the same day, allergic phenomena developed, associated with extreme congestion of the alveolar capillaries, which led to such intense dyspnœa that death sometimes occurred. The animals which survived this reaction, however, lived longer than the control guinea-pigs which had received only the intra-tracheal insufflation. Tuberculous bronchopneumonia did not develop in the guinea-pigs which had received a primary subcutaneous injection of bacilli, but a catarrhal alveolitis developed, ending in diffuse interstitial sclerosis. The bacilli did not multiply to the same extent, and were consequently more difficult to demonstrate when the alveolar tissue was stained and examined microscopically.

These phenomena can be entirely explained on the basis of an anaphylactic reaction leading to that immunity which it confers on sensitised subjects. This immunity is not absolute, being powerless to prevent the effects of a massive secondary inoculation.

Conclusions as Regards Allergy.

From the considerations just discussed we may conclude that the allergic state consists in the acquisition

by the body fluids of certain properties of an anaphylactic type, which are conferred by products of bacillary origin. These properties explain why a subject who has received a primary inoculation with such bacillary products tends to react violently to a second inoculation. The type of immunity engendered in this way is produced just as readily in tuberculous subjects as in subjects who have been inoculated with the bacillary proteins only, and not with living organisms.

Although allergy is not always an indication of tuberculosis, it invariably denotes the presence of an anaphylactic state, and resistance to any fresh inoculation. Allergy has been wrongly regarded as a predisposing factor, owing to the fact that allergy and tuberculous infection have been confused. It is the infection itself which predisposes to acute exacerbations of the disease.

A Few Problems relating to Allergy and Re-infections.

(a) *The Allergic Reaction in Children of Consumptive Parents.*—To disprove the theory that tuberculosis is transmitted congenitally, attention has often been drawn to the fact that the new-born children of tuberculous parents do not generally react to tuberculin. CATTANEO, however, and afterwards MIOCHE, were able to obtain positive reactions (within the first twenty-six days of life) in 29 per cent. of infants with tuberculous mothers, and in 18 per cent. of infants whose mothers were clinically sound. If the mother is free from the disease, how can her infant show a positive tuberculin reaction unless tuberculosis has been transmitted from the father?

ARONADE, FEER, HAYEK, IBRAHIM, MANGIALLI, POLLAK, SCHLOSSMANN, SIEGERI and others have taught us that infants showing a negative skin reaction at birth, if segregated immediately from their infectious parents and placed in an environment free from tuberculosis, with exercise of the strictest possible precautions to avoid infection, will still show, at

the end of a few weeks or months, an undoubtedly positive tuberculin reaction.

In a rural investigation covering 3,182 subjects, PHELEBON found that the skin reaction was positive in 883 cases (27.7 per cent.); according to age, these were distributed as follows¹ :—

Under 18 years of age	7.29 per cent.
Between 18 and 19 years	24.0 „
At 20 years	47.02 „
At 21 years	52.87 „
At 25 years	61.65 „

From these data it would appear that the development of the specific reaction of the body fluids is delayed to some extent in rural areas.

Expressing a view which at first sight seems to be opposed to the foregoing, FERRAN has always held that when animals have been prepared by injections of non-acid-fast bacilli, the tuberculin reaction does not develop. RAVETLLA and PLA Y ARMENGOL also inoculated animals of different species, including guinea-pigs, goats, dogs and horses, with a special stock vaccine in which the tubercle bacilli were present in a non-acid-fast coccal form; they failed to find any evidence of a specific tuberculin reaction in the animals treated.

Animals inoculated with filtrates obtained from tuberculous products vary in their sensitivity to tuberculin; this, at least, is what the experiments of BOQUET, NEGRE and VALTIS seem to show. With infants vaccinated with B.C.G. the reactions obtained are very variable.

To sum up, when the infecting bacillus is not acid-fast, the sensitisation of the body fluids does not appear to occur, or else is variable. On the other hand, it sometimes happens that cases of tuberculosis, even cases in which the disease is showing rapid progress, give negative reactions; that is why CALMETTE quite rightly concluded that: "A positive

¹ PHELEBON DE MONTRICHARD. "La Primo-infection tuberculeuse, est-elle toujours une Maladie de l'Enfance? Une Expérience rurale." *Presse Médicale*, Sept. 17, 1927, p. 1131.

tuberculin reaction can no longer be regarded as evidence of tuberculosis."

From these findings it is clear that positive skin reactions, comparatively rare during infancy, increase in frequency with age. How is this conceivable, apart from infection? We have seen that when the tubercle bacillus is not used in its acid-fast, adult form it will not sensitise the subject; now, this is precisely what happens in subjects inoculated with the filtrable virus, or with bacilli of low virulence, derived from persons suffering from a latent form of the disease.

In the country, where the development of latent lesions may be retarded by an open-air life, the appearance of a positive skin reaction will occur later than it does in towns.

The allergic state, therefore, appears to have two origins:—

(1) It appears in the children of consumptive parents, whether they are segregated from their parents or not, as soon as the saprophytic organisms which they have carried since birth assume the acid-fast form. These allergic subjects, affected with the disease will, as time goes on, either succeed in destroying the organisms which have been transmitted to them congenitally, or will develop a chronic, polymorphic form of the disease, which is the common form among the large bulk of consumptives.

(2) The allergic state may also appear in subjects not affected by the disease who have, at some time, received an inoculation of bacillary proteins which has induced an anaphylactic condition of the body fluids, and conferred a certain degree of immunity upon them.

(b) *The Effect of Tuberculin Injections on Tuberculous Patients.*—These effects are triple: local, focal and general. To explain them I may well refer to the experiments of a well-known bacteriologist, MARMOREK. He injects a small amount of a virulent culture of tubercle bacilli into a guinea-pig; a quarter of an hour later he injects 0.3 c.c. of tuberculin

into the animal, and keeps it under observation ; at the end of from three to five hours he finds the temperature rises to 40° C.

There can be no question, here, of instantaneous sensitisation ; there is simply a reciprocal reaction between the culture and the tuberculin in the presence of the body fluids.

When tuberculin is injected into a consumptive patient, the maximum concentration of one of the reagents—namely tuberculin—will be found at the site of injection, and the maximum concentration of the other—namely the active culture of the bacillus—will be found in the tuberculous lesions ; it is at these two points, therefore, that we should expect reactions and precipitation to occur. The precipitates formed are of a protein nature, and lead to a leucocytic infiltration of the surrounding tissues ; this infiltration constitutes, at one site the local, and, at the other site, the focal reaction.

Moreover, that part of the tuberculin not precipitated at the site of injection (or possibly some of the individual constituents of this complex substance) would circulate in the blood, and encounter toxins and excretory products derived from the tuberculous lesions of the patient, and would form with them a non-flocculating precipitate ; this precipitate would produce, not shock, but a rise of temperature, comparable to that produced by the injection of the salts of certain metals. In addition to the pyrexia developed in this way, the exo- and endo-toxins of the bacillus are capable, like other heterogeneous albuminoid products, of acting as sensitising antigens and giving rise to true anaphylactic manifestations, with precipitation and shock.

In the innumerable experiments which have been carried out upon tuberculin reactions, it is sometimes very difficult to detect which phenomena are attributable to anaphylaxis, and which to the non-antigenetic reactions just considered.

Among the observers who have carried out research

on sensitisation by tuberculous products, I may refer to MOUSSU, SATA and WOLF-EISNER, MATSUMURA, BALDWIN and KINGHORN, WASSERMANN, BRUCK, NICOLLE, MARIE and TIFFENEAU, STATINEANU and DANIELOPOLU, BAIL, ORSINI, CALMETTE and G. PETIT, SELIGMANN and KLOPSTOCK. Passive anaphylaxis has been investigated by YAMANOUCHY, BAUER, BAIL, HELMHOLZ, AUSTRIAN, THIELE and EMBLETON, LESNE and DREYFUS, KRAUSE, LOWENSTEIN and WOLK, VALLARDI, NEUFELD and DOLD, BRUYANT and others.

Contradictory inferences have been drawn, at times, from the results recorded by these different observers, probably owing to the confusion between the pyrexial reaction and anaphylaxis; some of them have come to the conclusion that sensitisation does not occur from the fact that the heat-producing mechanism was not affected—and *vice versa*. Again, the tests in many cases were conducted under widely different conditions as regards dosage, time and preparations used, with consequent discrepancies in the results. It has been clearly established, however, that shock of the anaphylactic type can be produced by giving animals a preliminary injection of the antigenic substances obtained from cultures of the tubercle bacillus; these substances are complex, comprising exo- and endotoxins of a protein nature, as well as albuminoid material derived from the organic culture medium used to grow the bacillus. The great intricacy of the tuberculin reaction can be appreciated when not only the multiplicity of antigens, but the non-anaphylactic colloidal inter-reactions are considered.

With regard to true anaphylactic sensitisation, FRIEDBERGER and his colleagues ascribe the phenomena following the injection of tuberculin to an *anaphylatoxin* which they were able to prepare *in vitro* by mixing fresh guinea-pig serum with antigen. To obtain this preparation, tubercle bacilli were triturated in an agate mortar with the serum of a tuberculous subject, rendered inactive by heating to 58° C.; the mixture

was left in the ice-box for twenty-four hours and then centrifuged, and the bacilli washed with physiological serum; the mixture was then placed in the oven for an hour or two and then returned to the ice-box for a further twenty hours; the decanted liquor was then injected into guinea-pigs of less than 200 gm. weight, and the animals died within two or three minutes.

In the most masterly work ever written on tuberculosis CALMETTE pointed out, quite rightly, that anaphylatoxin could be obtained by treating guinea-pig serum with mineral or organic substances, including kaolin, sulphate of baryta, gelatine and starch; and that therefore it could not be considered as a toxin, and the phenomena which it produces are the indications of a change in the physical state of normal serum, brought about by the absorption of the protective substances normally present in fresh serum.¹

I have formally demonstrated that these phenomena are not due to anaphylatoxin or to some protective antagonistic substance in the blood, but to the interaction of the serous colloids with highly divided solids, as a result of which inert particles, extremely minute in size, form a suspension in the medium, and suffice to produce the symptoms of shock; the intensity of these symptoms depends on the size, form and abundance of the particles in suspension. In fact the mixture must be centrifuged at a high speed for a long time before it loses its toxicity.² The process of separation is tedious because the density of the emulsified particles is not far off that of the serum.

On the whole, the reaction to tuberculin is highly

¹ A. CALMETTE. "L'Infection bacillaire et la Tuberculose, chez l'homme et chez les Animaux." Paris: Masson, 1928, 3rd édition, p. 567.

² AUGUSTE LUMIÈRE and H. COUTURIER. "Considérations sur le Sérum gélosé." *Arch. Internat. de Pharmacodynamie et de Thérapie*. Gand: 1925-1926. "Toxicité du Sérum en contact avec l'Amidon." *C. R.*, 1926. "Action du Kaolin sur le Sérum gélosé." *C. R. Soc. de Biol.*, 1926. AUGUSTE LUMIÈRE. "Le Problème de l'Anaphylaxie." Paris: O. Doin, 1924.

complex but can be interpreted in what seems to be a satisfactory manner by keeping in mind the fact that not only anaphylaxis but the inter-reactions of antagonistic colloidal substances, with resultant precipitation, are brought into play.

(c) *Resistance to Generalised Spread in Subjects who have been affected with Benign Local Tuberculous Lesions.*—

A certain amount of credence is often given to the notion that persons who have recovered from local tuberculous lesions—affecting the glands, skin, bones or pleura—afterwards show a special resistance to tuberculosis; this idea has even been set up as a principle, known as MARFAN'S law, which is read as meaning relative immunity. A number of facts recorded by MARFAN appear at first sight to confirm this theory; on the other hand, a number of clinicians affirm that people who have shown tuberculous manifestations at any time during the course of their lives are more disposed than other people to be attacked by the disease.

As a matter of fact a large proportion of consumptives give a history of an attack of pleurisy from which they recovered, five, ten, fifteen or twenty years before they developed progressive pulmonary, tuberculous lesions. In a thesis delivered in Paris in 1928, FREY stated that, while investigating the after-history of patients treated at Berck during infancy for local lesions from which they recovered, he found that one-fifth had ultimately died of pulmonary tuberculosis. If a first attack of the disease really protected patients against a second invasion, why do physicians repeatedly urge the parents of cured children not to relax their vigilance, but to maintain the strictest sanitary precautions, especially at puberty and during adolescence, in order to prevent recurrence of the disease? It is because the physician, far from relying on an immunity resulting from the early infection, has learned from experience that, on the contrary, such patients are more liable than a sound person to suffer from another attack of the disease.

This view is in complete agreement with my experiments, repeated hundreds of times and invariably affording evidence that susceptibility to the disease is increased by a first attack.

(3) *Tuberculosis in Negroes.*

As regards allergy, the conventional argument has often been put before me that the native population of Africa, who are not exposed to those small doses of tubercle bacilli which produce the allergic state, develop tuberculosis of a special type, very rapid in its progress. The habit of considering infection to be an established fact has blunted, in this respect as in others, the critical faculty of many medical men. Many of the factors involved in the problem have been ignored, and the medical profession has been content with an explanation which, although it did not exhaust all the questions which arose—or *because* it did not exhaust them, to put it more precisely—fitted in with the accepted creed. Since then every publication and work on the subject has been strictly orthodox. . . . Shades of Rabelais! One cannot help being reminded of Panurge's sheep, which followed their leader so blindly that they leapt after him into the sea and were drowned.

In the first place, it does not seem accurate to me to say that the native population of Africa is so completely free from tuberculosis. R. MOUCHET, on post-mortem examination, found tuberculosis lesions in 36.7 per cent. of coloured people of all ages.

In countries with a negro population tuberculosis often passes undetected because for a long time it is confined to the glands. The tuberculous Senegalese, for example, develops a characteristic facies recognisable by the muscular wasting and the dry scaliness of the skin; and the hilar lymph glands are found to be caseous in 80 per cent. of cases.¹

¹ A. BORREL. "La Tuberculose chez les Sénégalais." *Annales de l'Institut Pasteur*, 1920, p. 10. TOULLEC. "Les Aspects cliniques de la Tuberculose chez les Sénégalais." *Sud Médical et Chirurgical*, July 15, 1930, p. 438.

During the whole of the first phase of tuberculosis in the African native, the lungs remain unaffected ; the patient does not cough or expectorate, so that the disease remains unsuspected during this period, which may last for years, during which he remains unsupervised. Ultimately the bacillus passes into the blood-stream, pulmonary tuberculosis supervenes, and runs a severe and rapid course in a soil profoundly altered by the previous condition. In all this, allergy plays no part, and the argument which I quoted at the beginning of this section is based on an incomplete study of tuberculosis in these primitive people, and consequently upon an error.

Why should tuberculosis differ in different races ? This is a problem which clinicians seem to have neglected as lacking in interest ; but far from being devoid of importance its study will contribute to a better knowledge of the disease and a more thorough understanding of the defences which the body puts up against it.

I have tried to throw some light on this problem, and suggest that the following explanation fits in fully with the ascertained facts. The negro, unlike most Europeans, does not lead a sedentary life, nor does he spend his childhood and adolescence shut up in schools ; his food is utterly different from ours ; he does not eat meat or elaborate indigestible dishes twice a day, nor does he take alcohol daily. He feeds largely on fruit, lives in the open, and has regular actions of the bowels.

What happens ? The overburdening of the stomach which occurs almost daily in Europeans, the gastro-intestinal troubles, congestion and irritation of the intestinal mucous membrane, mild or acute alimentary intoxication, or self-intoxication due to constipation, and other discomforts of the same kind, do not occur or occur rarely in negroes. Assisted by such conditions as those set out above, the micro-organisms of the intestine, chiefly septic in Nature, manage to penetrate, in Europeans, the barrier which a sound mucous

membrane should oppose to them ; they reach the mesenteric lymph-glands, causing first an inflammatory reaction, and later the early lesions of sclerosis.

On this page (fig. 5) a mesenteric gland is shown, taken from an adolescent in perfect health who was accidentally killed ; the gland was no more than a damaged sieve which might eventually have

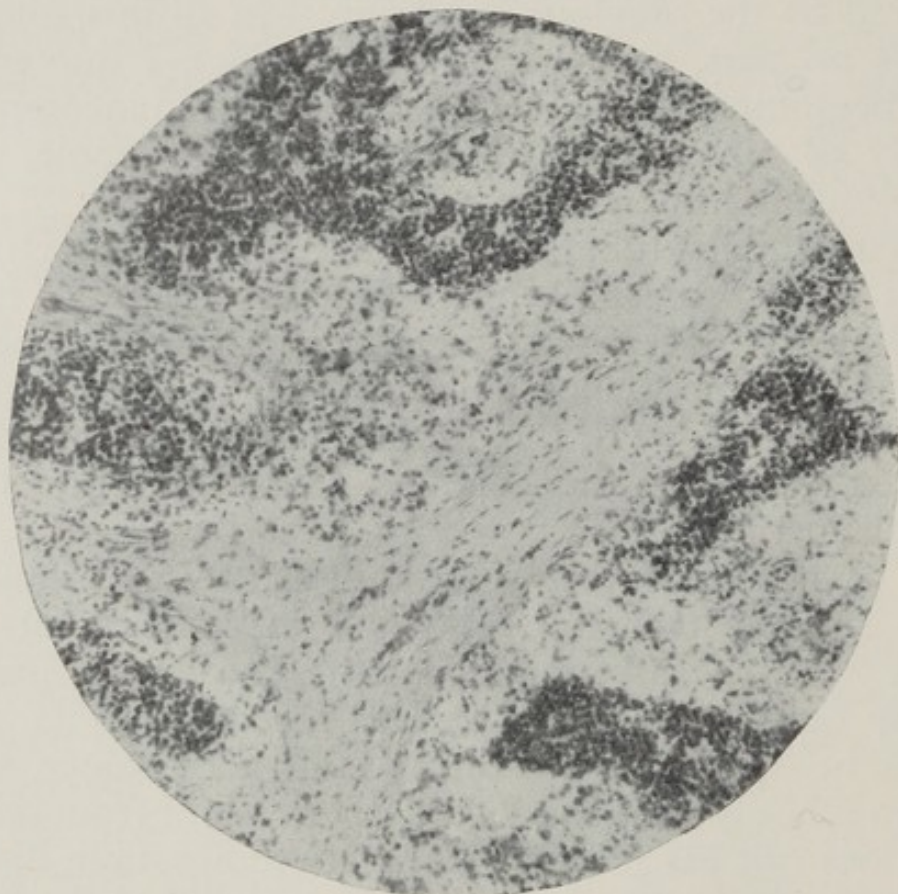


FIG. 5.—Mesenteric lymph gland from a European, 17 years of age, killed accidentally. Sclerosis and permeability to micro-organisms.

allowed KOCH's bacilli access, first to the neighbouring glands, and then by way of the venous circulation to the lungs where they would give rise to phthisis.

The mesenteric lymph-glands of negroes are not exposed to the same risk of degeneration ; they continue to do their duty, barring the way to micro-organisms as the lymphatic glands do in infancy, and this explains why these native races develop gland tuberculosis of the infantile type.

It is not impossible that certain histological conditions of the tissues and certain reactions of the body fluids play some part in determining the form the disease takes.

But it is none the less true that the common change in the lymph-glands has a marked influence in the circumstances discussed above.

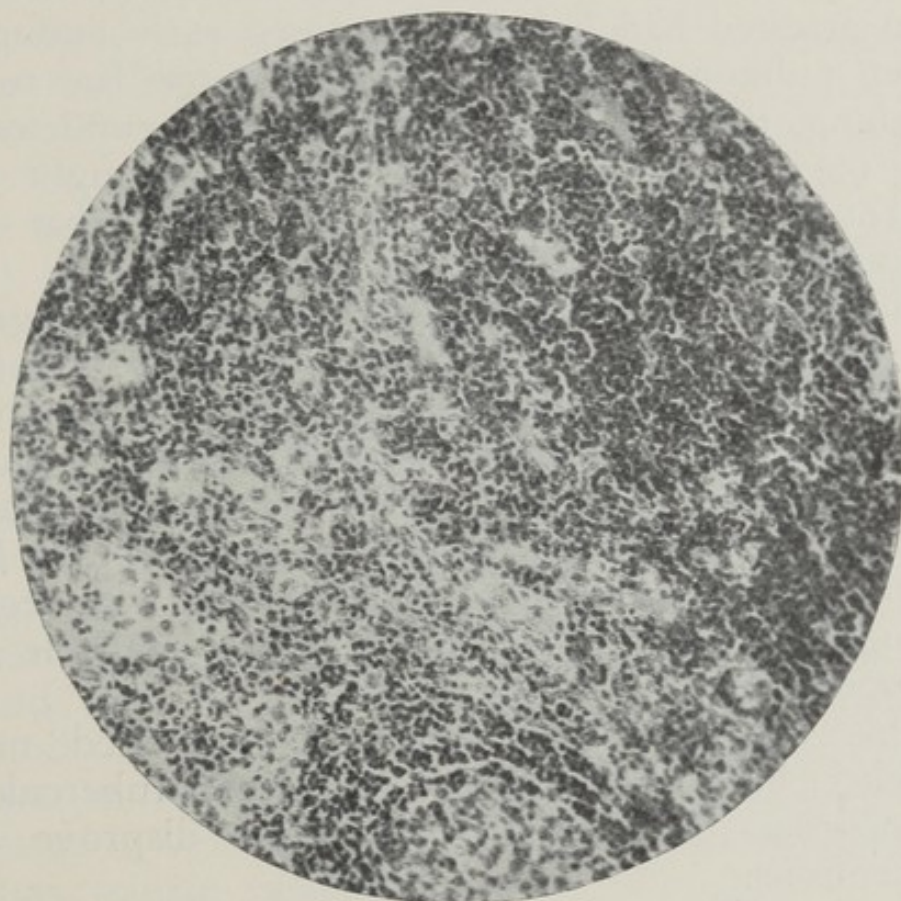


FIG. 6.—Normal mesenteric lymph-gland from a new-born infant.

This explanation is so plausible that in the large modern African cities, where the simple, rustic life of the past has given place to the nerve-racking and bewildering rush of European cities, the native population eat the same food as the Europeans, and alcoholism in negroes leads to the development of the same type of tuberculosis as is found in alcoholic Europeans.

L. Couvy, it may be well to recall, addressing the *Societe de Pathologie Exotique* in 1927, said that in

Dakar tuberculosis is at present developing on the lines of European tuberculosis, among the native population, and not in the form of glandular tuberculosis as in the past.

BORREL has also offered an explanation of the galloping type of consumption which appears to affect certain negroes. "In 50 per cent. of the Senegalese cases," he thinks, "the disease could have been arrested had it been diagnosed early enough." When pulmonary lesions appear it is too late to do anything, the glandular condition, often undetected and of prolonged duration, having brought the patient into such an unfavourable state that any attempt to fight the disease is impossible.

Since hearing of these cases of the disease in negroes I have been anxious to obtain accurate information about the subject, but have found hardly anything except unsupported assertions which neglect the most important aspects of the problem. It was, of course, no more than I expected. Could one hope to find precise clinical and demographic records with regard to negroes when no such data are available for European races?

This question, then, must be examined more closely; but I can safely state that tuberculosis in negroes offers no argument to disprove my conceptions.

Conclusions on the Clinical Facts relating to Infection between Adults.

I believe I am justified in drawing the following conclusions from this long discussion on conjugal tuberculosis and infection through cohabitation:—

(1) If tuberculosis is infectious between adults, we must ask for some explanation of the fact that the association between married persons does not appear to increase the chances of the partner who is free from tuberculosis acquiring the disease; and of the fact that tuberculosis specialists, male and female

nurses, and hospital sanatorium attendants are no more liable to acquire the disease than those who never come into contact with consumptive patients.

(2) All the observations quoted in support of the theory of infection are open to question because no precautions have been taken, in any of them, to prove that heredity or a hereditary tendency has not played a part in producing the disease.

(3) Since married life offers conditions which should be particularly favourable to the transmission of the disease, if tuberculosis is infectious between adults, infection must occur very rarely; and in any case there is no convincing proof that it occurs at all.

(4) In order to settle the question once and for all, thorough investigation of the family history of married couples and of people living in close association with tuberculosis would provide data of the utmost interest; from such data it would then be possible to determine definitely the cases in which there was no hereditary factor involved in the production of the disease.

Statistics of conjugal tuberculosis and mortality should also be collected, with the details of the method on which they were compiled; and a comparison should be made between them and statistics collected in other countries. As long as these investigations remain unattempted, doubt must still exist of the occurrence of infection between adults; the arguments so far quoted in support of it are too vague and incomplete, amounting for the most part to idle speculation without any scientific foundation.

(5) On the other hand, a large number of facts appear to disprove the theory that infection occurs between adults; these facts must be accounted for if the theory of infection is to continue to hold the field as the chief, if not the only, method of transmission of the disease.

(6) To sum up, I find myself unable to accept the conventional theory of infection in adults as anything but a rarity, and shall continue to doubt as long as

the objections I have raised remain unanswered, and as long as the only arguments produced against them consist of the unsubstantiated stories with which transient opinion has been so easily satisfied hitherto.

I believe, besides, that I have thrown some light on the obscure problems of allergy and of tuberculosis among negroes, upon which, without any sound reason, attempts have been made to found arguments in support of the theory of infection.

CHAPTER IV.

INFECTION (*continued*).

ARGUMENTS based on experimental evidence :—

A. Inoculation.

When VILLEMEN, on December 5, 1867, reported to the Academy a series of experiments in which he had succeeded in infecting animals by injecting them with caseous material from tuberculous glands, the supporters of the theory of heredity were dismayed ; their rout was completed a few years later when KOCH discovered the offending organism, and subcutaneous injections of pure cultures of tubercle bacilli were found invariably to produce infection in guinea-pigs.

Transmission of tuberculosis by injection of the organism under the skin, which undoubtedly occurs in animals, can occur equally well in man, as a number of intentional and accidental cases of inoculation have demonstrated. Medical literature, as far as I know, contains only two examples of intentional inoculation : the first was the case of a young man who, in despair at seeing his sweetheart succumb to consumption, injected himself with her sputum and died of the disease a few months later ¹ ; responsibility for the second case lies upon three Greek medical practitioners, Dr. DEMET, Dr. PARASKOVA and Dr. ZABLOVIS who, during the year 1871, in defiance of the Hippocratic oath, inoculated the sputum of a consumptive patient into the right thigh of another patient, aged 55 ; the second patient, who was suffering from gangrene

¹ P. JOUSSET. "La Prophylaxie de la Tuberculose," p. 19.

of his left foot, died 38 days later, and post-mortem examination revealed the presence of 17 small tuberculous nodules at the apex of the right lung, 2 on the apex of the left lung, and 2 more on the convex surface of the liver.¹

Cases of accidental transmission, as a result of tubercle bacilli being carried into wounds, are more numerous, but are none the less infrequent, and can readily be enumerated. Doctors, who are liable to acquire such accidental lesions, particularly in performing autopsies, furnish most of the statistics in this group.

Let us recall in more detail the facts summarised in the preceding chapter. The first case is that of Dr. TORKOMIAN who, in 1882, when performing a post-mortem examination on a patient who had died of generalised tuberculosis, pricked himself and developed a local abscess associated with swelling of the epitrochlea and axillary lymphatic glands. After evacuation of the abscess fleshy granulations persisted for some weeks, and ultimately disappeared following the application of silver nitrate. The patient showed no signs of tuberculosis six years after the accident.

While performing autopsies on consumptives, the eminent surgeons MAISONNEUVE and VERNEUIL also gave themselves slight injuries, and each developed, at the site of the prick, a typical tubercle, which took about a year to heal. Neither of them had become tuberculous thirty-eight years afterwards. Prof. CHAUVEAU also acquired a tuberculous lesion at the site of a small wound obtained during the post-mortem examination of a patient with miliary tuberculosis; and eighteen years later there was no evidence that this local lesion had given rise to any unpleasant sequelæ.

Scores of similar cases could be quoted, but would throw no further light on the subject.

In addition, however, to these examples of a local

¹ *Dictionnaire de Médecine et de Chirurgie Pratiques*, p. 621.

lesion progressing to complete recovery, there are others in which generalised infection followed. Among these may be included the case of LAENNEC, who died of tuberculosis at the age of 45, more than twenty years after he had developed a local tuberculous lesion as the result of an infected prick; it must be remembered, however, that the famous clinician's mother died of pulmonary tuberculosis when he was six years old, so that, in his case, heredity may be implicated.

JEANNEL records the case of a woman who, in the course of looking after her tuberculous child, acquired a local tubercle, and subsequently developed chronic bronchitis which proved fatal; this has been claimed as an example of the reversal of heredity, but I am more inclined to think that the mother, suffering from one of the common latent forms of tuberculosis, went gradually downhill, and that the local lesion and the condition of the child did not influence the course of her disease.

VERCHERE, in his Paris thesis of 1884, referred to the case of a medical student in whom an accidental cutaneous inoculation gave rise to a local tubercle, and subsequently to generalised tuberculosis which carried him off, but it should be noted that the father of this patient was tuberculous.

It is singular that when a local tuberculous lesion of the kind under discussion fails to heal and gives rise to generalised infection, the patient usually comes of tuberculous stock. One may well wonder whether the generalised spread is not independent of the local lesion. Indeed, at the Tuberculosis Congress of 1888, BARTHELEMY had no hesitation in stating: "I have observed no case of general or visceral tuberculosis following a local traumatic tubercle, whether the local lesion is left alone or treated surgically."

To regard such an assertion as axiomatic would no doubt be a mistake; cases do seem to occur, in point of fact, in which the infection spreads from the

local lesion. It remains to determine what conditions are necessary to cause either a general spread of the infection or the complete recovery of the local lesion.

Another mode of infection, the consequences of which are serious and often fatal, is that to which Jewish infants are exposed at the rite of circumcision ; certain rabbis, who may be in a state of advanced tuberculosis, suck the wound in the prepuce to check hæmorrhage. The literature on this subject has been summarised by STRAUS ; DUBREUILH and AUICHE described the course of the disease and the lesions which characterise this form of tuberculosis. The infected wound fails to heal, or healing is inadequate ; nodules appear at the site of the wound, and rapidly ulcerate, the ulcers spreading and becoming confluent ; the inguinal glands become swollen and ulcerate in their turn ; cold abscesses develop in various parts of the body, and the infant wastes, becomes cachectic and dies in a few months. Occasionally, however, recovery occurs in spite of these multiple lesions.

From the foregoing it may be inferred that tuberculosis is transmissible to man and animals by the massive subcutaneous inoculation of bacterial products or cultures. If inoculation occurs accidentally, as a result of a wound, a specific local lesion may arise which usually heals if the patient does not come of tuberculous stock. When the patient is the child of tuberculous parents it is impossible to say whether the secondary infection, of which he is the victim, has any influence on the progressive condition from which, in some cases, he may die. Transmission of the disease in the course of the rite of circumcision is particularly serious.

For the most part, however, infection by accidental subcutaneous inoculation, although it occurs, affects only a small number of persons, and is negligible as an ætiological factor in comparison with the large numbers of cases in which it plays no part. The experiments and observations described above have

been gravely misinterpreted by those who regard them as being of common occurrence and who confuse inoculation with infection. Some writers have realised this and have instituted experiments under conditions more comparable to those encountered by the human subject in a tuberculous environment.

B. *Infection by Inhalation : Expectoration.*

The lesions of tuberculosis in the lungs being in communication with the bronchi, the tubercle bacilli are either projected in the saliva in the form of droplets of varying size when the patient speaks, coughs or sneezes, or are expectorated in the sputum ; in the latter case, before the bacilli can reach the bronchi of a second person, the sputum must fall on the ground, dry, and the bacilli must then become suspended in the atmosphere so that they are inhaled by the threatened individual.

Let us see what takes place with these two methods of dissemination of bacilli, and let us analyse the experiences arising out of them.

(1) *Droplets projected in Coughing.*—Sometimes called the droplets of Flugge, after the observer who studied them closely, these particles composed largely of saliva and expelled by the patient, are infected in about 50 per cent. of cases ; the distance to which they are projected varies, as a rule, from 40 to 80 centimetres. According to ZIESCHE, 80 per cent. of patients project, in this way, between 700 and 800 bacilli per hour, and in 20 per cent. of cases the figure ranges from 800 to 40,000 per hour.

The size of the droplets usually varies between 100 and 500 microns, and they are seldom smaller than 30 microns ; when droplets with smaller dimensions than this are found—which is exceptional—they contain no bacilli. But only those droplets which do not exceed 15 to 20 microns are capable of remaining suspended in the air sufficiently long to be inhaled. It is clear, then, that it is almost impossible

for bacilli expelled in this manner to find their way into the lungs of another person. Theoretically, however, the projection of droplets in coughing constitutes a mode of infection, since the bacilli may be deposited directly on the ocular, labial or buccal mucous membranes of a second person. Practically, the risk appears to be negligible, at any rate for adults, since, if these droplets were dangerous, all consultants attending tuberculous patients would be dead or dying—whereas I have never heard of one who was infected in this manner.

(2) *Expectoration*.—The numbers of bacilli disseminated by droplet infection from patients (in coughing, sneezing and pronouncing certain consonants, especially labials) are trifling compared with the enormous numbers of bacilli which may be present in the sputum. It is, therefore, to the investigation of infected sputum that the attention of pathologists has been principally directed. The most virulent bacilli are naturally to be found in fresh sputum, prior to desiccation, and the first question was to decide whether the organisms could be detached by blowing a more or less powerful current of air through the expectorated mass. Observers next tried to infect animals by causing them to inhale air which had been passed through heavily-infected sputum. In one test a current of air was passed through sputum at the rate of 35 metres per second; but of 165 guinea-pigs permitted to breathe this air only one developed tuberculosis. CHAUSSE, who increased the velocity of the air current up to 80 metres per second, obtained entirely negative results with his animals.

Under ordinary conditions of life, of course, sputum is never exposed to powerful air currents, and no infected material can escape into the atmosphere as long as the sputum remains moist; as long as this condition holds, no tubercle bacilli from the sputum can find their way into the lungs of persons in the vicinity. Let me add that if desiccation occurs while the sputum is exposed to light, the bacilli

lose not only their virulence but even their power of inducing tuberculosis. On this account expectoration is, for the most part, harmless. Moreover, CHAUSSE has shown that sputum which dries in the dark has little virulence at the end of 24 hours, and is completely innocuous after ten days.

The bacteriological investigations carried out by WEHDE, GUARNIERI, BAUMGARTEN and CORNET, with a view to detecting infected dust on premises occupied by consumptives, have always been negative. KELSCH went further and inoculated into guinea-pigs particles of dust, collected from chinks in the floors, the corners of walls and staircases and the rims of spittoons; 121 animals were inoculated but none of them became tuberculous. JOUSSET concludes from these experiments that it is extremely difficult for man to contract tuberculosis by breathing an atmosphere containing, in suspension, particles which are incapable of producing the disease in guinea-pigs *by inoculation*.

A fortiori, if guinea-pigs are allowed to live in the same premises as consumptives, they will never become tuberculous, though these animals are particularly susceptible to the disease. Inhalation of the atmosphere in consumptive wards not being accepted as providing conclusive evidence, many observers undertook experiments in which they deliberately exaggerated the conditions favourable to infection, by placing their animals in an environment which was completely abnormal. Sputum was dried at a low temperature and in the dark, and the powder obtained in this way was used either in a dry or moist condition, to spray the cages of the experimental animals, or as an insufflation which was blown into the trachea of each guinea-pig in turn.

PETERSEN, BAUMGARTEN, SANTO-SIRENA, PERNICE and DI TOMA placed guinea-pigs in surroundings in which the air was loaded with dry bacillary dust; similarly, CADEAC and MEUNIER caused infected dust to be blown by means of bellows into the closed hutches in which their guinea-pigs were housed.

None of these observers succeeded in producing tuberculosis in the experimental animals; it was possible, however, to infect them in this way if experimental bronchitis was first induced by causing them to breathe an atmosphere containing hydrochloric acid gas. Although attempts to cause infection by placing the subject in an atmosphere loaded with dried tuberculous material constantly fail, tuberculosis can readily be induced by the deliberate insufflation of infected dust into the air passages of an animal or by spraying an emulsion of the bacilli into the trachea by means of an atomiser. Experiments of this kind have been carried out by CORNET, and his findings confirmed by CADEAC and MALET, CELLI and GUARNIERI, THAON, SOUZA and GALLOIS, TAPPEINIER, BERTHEAU, WEICHELBAUM, VERAGUTH, KOCH, FLUGGE, CALMETTE, PREYSS, HAMILTON and YOUNG, WEBER and TITZE, CHAUSSE, KOSSAL, COBBET, BRAEUNING, HOLLMANN, SANGER, LANGE, CESA-BIANCHI, KUSS and LOBSTEIN, NOCARD and ROSIGNOL and others. In this connection KELSCH writes: "No doubt M. CORNET has succeeded in inducing tuberculosis in guinea-pigs by the insufflation of dried sputum into the trachea, or by keeping the animals in an atmosphere laden with dust obtained by the energetic brushing of a carpet impregnated with the sputum of a consumptive patient; but these conditions are remote from those of real life. The infected particles were, so to speak, forcibly projected in massive doses into the respiratory passages of the experimental animal; and in any case, the fact that the animal was living in a thick cloud of finely-powdered virulent material constitutes an extreme exaggeration of the conditions created by the mere vicinity of a consumptive. Such experiments show that the guinea-pig can be rendered tuberculous, and nothing more. Pulverisation and insufflation of massive doses of the bacillus are modes of infection which never occur with human subjects."¹

¹ KELSCH. "La Tuberculose dans l'Armée," p. 32.

Under the usual conditions of life as lived by consumptive patients, infection of others through the respiratory passages hardly seems possible ; attempts to produce such infection experimentally, by permitting even the most susceptible of animals to inhale a tuberculous atmosphere, always end in failure.

C. Infection via the Alimentary System.

The numbers of micro-organisms in suspension in the air of localities which are likely to be heavily contaminated—that is to say, in the air of sick wards and crowded public places—have been found to range from 10,000 to 15,000 per c.c. ; yet people breathing such air remain free from infection ; bacteria fail to reach their lungs, being arrested and destroyed before they can penetrate to the alveoli. (BARTEL, BONI, EMMERICH, MULLER, KLIPPSTEIN, QUENSEL and ARLO.) But this does not mean that micro-organisms cannot penetrate the system in other ways.

Experiments and observations designed to show that tuberculosis can be acquired by way of the alimentary system are so numerous that I must content myself with recalling only a few.

(a) *Experimental Feeding with Tuberculous Products and Cultures.*—In 1893 MALIN recorded that two dogs which had swallowed the sputum of a tuberculous patient subsequently succumbed to widespread pulmonary lesions. Remembering that some consumptive patients expel upwards of 7 billion tubercle bacilli daily in the sputum, we can form some idea of the enormous dose of bacilli ingested by these animals. The observation does not prove much as regards infection by way of the alimentary tract in man, under normal conditions of life, since no sane person would swallow the sputum of a consumptive. The same objection applies to most of the experiments designed to demonstrate the possibility of infection by this route.

The earliest experiments of the kind were performed

by CHAUVEAU between 1868 and 1872, and they are among the most interesting and significant. His results were confirmed by VILLEMIN, PARROT, KLEBS, GUNTHER and HARNS, SAINT-CYR, VISEUR, TOUSSAINT, PEUCH, BAUMGARTEN, WESENER, PERRONCITO, SIDNEY-MARTIN, SCHOTTELIUS, NOCARD and ROSSIGNOL, HAAN, VALLEE, CALMETTE and others, who infected various animals through the same channel (including guinea-pigs, rabbits, dogs, swine, sheep, goats, oxen and monkeys) by means of pure bacillary cultures or the material from tuberculous lesions.

The conclusions reached from these investigations may be summed up simply as follows: ruminants are more susceptible to infection than carnivores, and in any given species young subjects are the most readily attacked.

VON BEHRING and ROEMER, BISANTI and PANISSET, FICKER, OBERWORTH and Lydia RABINOWITSCH found tubercle bacilli not only in the lymph-stream but in the blood of the heart after the experimental animal had received an infected meal, and the younger the animals used the higher was the percentage of positive results. Passage of the bacilli into the general circulation does not imply, however, that tuberculous lesions would necessarily have followed, since bacilli may lose their virulence or be removed by diapedesis—phenomena which have been frequently observed and need no emphasis.

The passage of organisms into the lacteals appears to be favoured by the digestion of fats; DESOUBRY and PORCHER showed that this was the case with micro-organisms in general, and NICOLAS and DECOS showed that it was also true of KOCH's bacillus. SCHLOSSMAN and ENGEL, and ORTH and Lydia RABINOWITSCH made use of this fact in their investigations by feeding their experimental animals on bacillary emulsions prepared with cream.

Yet in spite of massive and repeated dosage, attempts to produce infection have failed in many cases. It is

worth noting that the spontaneous infection of animals living on the same premises as consumptives has never been shown to occur ; this is important, since we are not in the habit of seasoning our food with KOCH's bacilli or tuberculous material.

Nevertheless, tubercle bacilli may contaminate food accidentally, as occurs with tuberculous milk or meat from tuberculous animals.

(b) *Tuberculous Meat*.—At the Tuberculosis Congress in 1888, BUTEL asked and answered the following questions :—

“Is it dangerous to eat the flesh of tuberculous animals ?” “Yes.”

“Is the risk great ?” “It is enormous, because not only is the flesh of large numbers of tuberculous animals sold for food, but a single animal may infect a large number of consumers.”

What evidence did this observer submit to the Congress in support of his categorical assertions ? None. What grounds had he for being so dogmatic ? His statements had no foundation at all. The members of the Congress, however, do not seem to have objected to his opinion.

Although a historical survey of the experiments carried out on infection would include many other observations, it would consist for the most part of impressions of the kind I have just quoted, and would have no scientific value.

Contrary to BUTEL, BROUARDEL, one of the disciples of the theory of infection, declared in 1890 that no harm would result from eating meat obtained from animals affected with localised tuberculosis ; and STRAUSS, arguing from facts which are as illuminating as any experiment, showed finally that meat derived from tuberculous cattle is harmless.

GALTIER, professor at the Ecole Veterinaire at Lyons, was unable to infect animals by feeding them with raw meat obtained from tuberculous cows. JOUSSET tells us in his book that in 1867 and 1868 the authorities of the city of Wursburg authorised

the sale of meat from tuberculous cows to the residents of certain districts, who were invited to use it under the supervision of Dr. REUBOLD and Dr. HAEKER. The meat was used in various ways, cooked, roasted, as sausage meat and even raw, week after week under medical control. At the end of the year no cases of infection had been recorded, and subsequently tuberculous meat was supplied as food to destitute persons. Fifteen years later a census was taken of the mortality and morbidity in the families which had used such meat regularly; 130 persons were involved, and 11 deaths had occurred among them, not one of which was due to tuberculosis. BOLLINGER conducted a similar inquiry in Bavaria, covering a group of 300 persons, knackers and their families, among whom the use of tuberculous meat is quite common; he found the incidence of tuberculosis among this group of people to be lower than elsewhere.

It does not appear, then, that the meat of tuberculous cattle can be regarded as a potent factor in the transmission of tuberculosis.

(c) *Infection through Cows' or Goats' Milk.*—On the other hand, milk obtained from cows or goats affected with tuberculosis of the udder will readily infect the animals that consume it, as the experiments of BARTEL and CALMETTE have shown—experiments which I shall presently consider more at length. If tuberculous milk is capable of infecting ruminants, is it equally harmful to the human species? JOUSSET questions this, and since the criticisms (sometimes biting) which he offers of the accepted view are in some respects suggestive, I will take the liberty of quoting his views verbatim on this point; I do so the more readily since no attempt has been made to introduce the corrections which he demands.

“A few years ago,” he writes, “the theory that infection with KOCH’s bacillus could be transmitted by means of the milk of tuberculous cows was regarded as an axiom which no one dared to question; and since cheese and butter made with the milk of

tuberculous animals also contained KOCH's bacillus the following absurd formula was reached : Drink only boiled milk, eat no butter and cheese that has not first been melted. On what grounds, however, was this opinion actually based ? On an erroneous interpretation of experimental facts : the milk of tuberculous women, tuberculous cows' milk, and butter and cheese made from tuberculous milk are liable to cause tuberculosis when inoculated into guinea-pigs. The error consists in identifying the conditions found in guinea-pigs with those found in man, and in assuming that transmission of the disease by the ingestion of tuberculous material bears any relation to the much more effective method of transmission by infection.

"As for clinical evidence in 1889, I contended that none existed ; I added that if facts were lacking in support of the theory that tuberculosis could be transmitted by cows' milk, there were plenty of unsupported statements and anecdotes on the point.

"At the Tuberculosis Congress in 1888, M. LEGROUX was the only medical practitioner who adduced a clinical fact intended to demonstrate the transmission of tuberculosis by milk. This particular fact was incomplete and inadequate. In order to demonstrate that tuberculosis can be transmitted by milk the following conditions are necessary :—

(1) KOCH's bacillus must be demonstrable in the sample of milk used.

(2) The first site of infection must be in the mesenteric lymphatic glands.

(3) Other opportunities for the transmission of tuberculosis must be absent.

"And now let us examine the facts :—

"Reference was made to a family of 5 children. The father and mother and the grandparents showed no evidence of tuberculosis (not even enlarged glands). Of the 5 children, 4 were healthy and robust. The second child had been breast-fed for the first few months of life, and after that had been

partly breast-fed and partly artificially fed. The milk used for artificial feeding was supplied by a dairy at which the cows, imported from Switzerland, were properly looked after, and spent part of their time out in the open. The manager of the farm admitted that after fifteen or eighteen months his cattle fell ill and had to be sent home. '*In all likelihood,*' LEGROUX added, 'long before getting rid of them the farmer would continue to sell their milk although it was already infected.' The child fed on this milk developed tuberculous meningitis at the age of twelve months, and died within twenty days. There is nothing to show conclusively that the milk given to the child contained KOCH's bacilli, or that the disease made its first appearance in the mesenteric lymph glands. This evidence is therefore open to question.

"But if scientific facts are scarce there is no lack of anecdotes. From M. NOCARD's Angora cat to the 13 young ladies who became tuberculous at a finishing school in Chartres, one meets with nothing but impressions instead of facts collected and reported in the spirit of serious criticism suited to such an important problem. The story of the consumptive girls at the Chartres finishing school beats M. NOCARD's Angora cat hollow. M. BROUARDEL has already made a guarded reference to the story; and the alleged facts, since contradicted, contributed not a little to the final vote of the Académie, regrettable in some respects, regarding the prophylaxis of tuberculosis (*Bulletin de l'Académie*, t. xxiii, p. 52).

"A few months after that vote, M. Auguste OLLIVIER obtained the complete facts of the case. He had attended a young lady, in Chartres, who succumbed to tuberculous meningitis; this young lady, whose parents were perfectly free from tuberculosis, had been a pupil at a finishing school in the town, and during the year 1887-1888, 4 pupils in the same school died of intestinal tuberculosis and 7 others, affected in the same way, recovered and are still under treatment. In addition, another girl died

of galloping consumption in 1890, making a total of 13 pupils affected with tuberculosis over a period of two years. For several years the school had owned a cow which was slaughtered in 1889, and was then found to be affected with *generalised tuberculosis* and *tuberculosis of the udder* (*Bulletin de l'Académie*, t. xxv, p. 288). 'Surely,' adds M. OLLIVIER, 'this is a perfect demonstration of the transmission of tuberculosis by milk, and proves the extreme importance of boiling milk before use.'

" 'Certainly not, M. OLLIVIER!' Dr. JOUSSET goes on to say; 'your communication proves nothing of the kind, because the facts were inaccurately observed; the paper which you read to the Académie had no scientific basis, but was founded on your impressions.'

" At the next session, M. OLLIVIER, better informed, reported the following facts: 'In the first place, the original case of meningitis could not have been due to the milk of the cow in question because the pupil had left school before the animal was bought; the 12 remaining patients could not have acquired the infection from the milk, any more than the first one, because the milk was never used otherwise than boiled, and was served mainly to the teaching staff, among whom no cases of tuberculosis occurred.' (*Bulletin de l'Académie*, t. xxv, p. 311).

" This correction having been made, my old colleague and friend, Dr. MOUTARD-MARTIN, was justified in saying, as he did: 'Before intimidating whole families, it would be as well to make sure of one's facts.' I am sorry to say that I found the original story quoted in the "Traité de Médecine" by BOUCHARD and CHARCOT, without any mention of the subsequent correction, so that a mistaken account of the facts has been disseminated throughout the medical profession under the patronage of two respected authorities.

" I am also sorry to have to point out that, in M. BROUARDEL's book, "La Lutte contre la Tuberculose,"

a similar distorted account is given of M. OLLIVIER's story, and I cannot help wondering how authorities whose credit stands so high could have thought themselves justified in misrepresenting facts reported to the Académie in such a way as to give them the opposite significance from that which they really bear. Without due consideration and without having sifted his information, M. OLLIVIER communicated a story to the Académie which seemed to demonstrate the transmission of tuberculosis by tuberculous cow's milk. An inquiry, demanded by the victims of this mistake, showed his inferences to be entirely erroneous. I cannot help thinking a man must be blinded by scientific passion if, with deliberate purpose to mislead, he is so unscrupulous as to make the facts appear to convey the reverse of the truth.

"To sum up, experiments on young animals fed for long periods on milk rich in tubercle bacilli have demonstrated that transmission of tuberculosis by milk is possible, and CALMETTE's experiments have shown this still more clearly ; but these observations prove nothing as regards the human species."

While, broadly speaking, I agree with Dr. JOUSSET in recognising that the evidence adduced in support of the theory of infection is notoriously poor and frequently put forward without sufficient consideration, I hope he will allow me to point out that infection of the mesenteric lymph glands is not an indispensable sign of infection by way of the intestine, as I will show later. Absence of infection from the mesenteric glands does not prove that intestinal infection did not occur. On the other hand, does it not seem rather strange that, in the same finishing school, 11 cases should have arisen all showing the same form of intestinal tuberculosis? This form of the disease is relatively rare, as compared with pulmonary tuberculosis, and the occurrence of 11 cases of this rather uncommon condition in a restricted group of subjects is decidedly perplexing.

Although I am disinclined to lay the blame on

infection, which I consider to be exceptional among adults, my scientific conscience compels me to admit that the facts, as ascertained, provide an argument which I cannot answer.

The chain of events under consideration involves young, and therefore relatively susceptible subjects, and the chances are that a single extraneous cause, acting under uniform conditions, did give rise to the same form of the disease in all these subjects. What could this cause have been? It is impossible to say for certain, and we can only speculate. Possibly some article of food, particularly rich in tubercle bacilli of a certain virulence, was eaten on the same day by all the boarders in the school, but this is merely a suggestion without any scientific basis, and consequently is open to question.

Certainly the explanation of the high incidence of tuberculosis is not to be found in the theory of transmission by milk; in fact the incidence of the disease is higher in countries where milk is not drunk, and therefore cannot be blamed. According to C. LANGE, over one-third of the deaths in Greenland are due to tuberculosis, although no milk is drunk there, not even the milk of reindeer, for these beasts do not form tame herds as they do in Lapland. It is perfectly evident, besides, that pulmonary tuberculosis is quite common in regions where tuberculosis of cattle never occurs, and children are not fed on cows' milk. In such areas the transmission of the disease must always be between human subjects.

Be this as it may, the problem of infection through the tuberculous milk of cattle, and the butter and cheese made from such milk, still awaits solution. In spite of the large quantities of these products consumed, they have so far furnished only rare instances of infection, and, moreover, these instances have never been thoroughly well authenticated.

The danger, if it exists, must be a mere matter of chance; but does it exist? *Adhuc sub judice lis est.*

(d) *What becomes of the Koch's Bacilli present in*

Tuberculous Milk when Casein and Butter have been separated?—In view of the possibility of infection by means of tuberculous milk, the reader will excuse me if I digress a little to summarise the evidence relative to the distribution of the bacilli in the components of separated milk. We are told to boil our milk, but we are not invited to boil our butter and cook our cheese. When tuberculous milk has been separated into its component parts, what becomes of the bacilli?

Several observers, more especially SCHROEDER and COTTON, HERR and BENINDE, OSTERMANN, BANG, ROTH, BROERS, COOKSON, HARRISON and KANKAANPA have examined various samples of cream, butter and cheese, made from tuberculous cows' milk, for the presence of bacilli. Although the organisms have been found, generally in a living and virulent condition, in these various derivatives of milk, observers do not agree on the relative numbers of bacilli found in the different products.

I have considered the question from another angle, with the collaboration of Madame DUBOIS, and have tried infecting a given sample of milk artificially with a homogeneous culture of tubercle bacilli, and examining the distribution of the organisms in the various products obtained from the milk. In this experiment, 10 c.c. of an 8-days' old homogeneous culture of KOCH's bacilli was added to half a litre of milk, and the mixture shaken to ensure uniform distribution of the organisms throughout the fluid; microscopic examination of a slide prepared with Ziehl staining showed the bacilli to be evenly distributed in the medium.

Butter was then prepared by two distinct methods:—

(1) By allowing the cream to rise for twenty-four hours in an ice-box, and then churning it, the whey being expressed afterwards by compression.

(2) By centrifuging the tuberculous milk for five minutes so that a thick cream was formed which only needed to be churned for a few moments to give butter.

In neither case was I able to find evidence of the presence of tubercle bacilli in the samples of butter produced.

Casein was also separated by two distinct methods :—

(1) By heating skimmed milk in a stove for twenty-four hours.

(2) By adding 3 drops of concentrated rennet to half a litre of skimmed milk.

In both cases a microscopic slide prepared with ZIEHL staining showed the presence of numerous groups of Koch's bacilli.

The whey was found to be devoid of bacilli, so that they must have been drawn into the casein network when the milk curdled; their inclusion in the curd was a mechanical process analogous to that which is employed in clearing wine.

According to these experiments, if there is a risk of infection through dairy produce obtained from milk, it is fresh cheese which offers the greatest danger to the consumer. I am aware that, in spite of my earnest criticism, the theory of infection will continue, on scientific and other grounds, to receive warm support; and I venture to draw the attention of those supporters of the theory who are interested in public health to the results of my experiments; if they consider them to be convincing will they have to recommend that cheese should be cooked before being eaten?

(e) *Infection through the Milk of the Mother or Wet-nurse.*—If tuberculous cows' milk is sometimes encountered it is due to the fact that tuberculous lesions are situated in the gland itself. With women, cases of this kind need scarcely be considered, since if a woman has tuberculous mastitis she is precluded from nursing her child. It was alleged for a long time that, apart from this condition, the milk of tuberculous women never contained tubercle bacilli. As a matter of fact, when pulmonary disease is advanced the milk may be contaminated. It is, therefore, only in those cases in which it is out of the

question to allow the mother to suckle her child that tubercle bacilli will be found in her milk.

A story is told of a woman who died from generalised tuberculosis seventeen days after delivery, having breast-fed her infant for three days. The child succumbed at the end of fifty days, and was found to have enlarged mesenteric glands and tubercles in the liver, spleen and kidneys. The inoculation of 4 c.c. of the mother's milk into a guinea-pig caused the death of the animal within thirty-three days.

GUILLEMET and RAPPIN also infected guinea-pigs by inoculating them with 2 c.c. of milk obtained from a consumptive woman. MOUSSU injected the clot obtained by centrifuging the milk of a tuberculous woman, and obtained only one positive result out of 10. Other tests of the same kind have been carried out by KURASHIGA, MAYEYAMA and YAMADA, with similar results. But in all these experiments milk was given by injection; whereas a mother's milk is never injected into a baby. Only the first case—that in which the mother breast-fed her baby when she was on the point of death—can fairly be regarded as evidence, and even this is susceptible of a more likely explanation. In view of the advanced state of the disease in the mother, and the fact that the child died within fifty days of birth, the probability is that the infant was born with congenital lesions; infected infants usually die after several months' illness (in the majority of cases after about eight months), and not within fifty days of birth.

In practice, while the danger may be real, infection seldom occurs, and should scarcely be taken into account when considering the transmission of tuberculosis.

Infection by Way of the Alimentary Tract.

When deposited on the conjunctiva or the nasal and buccal mucous membranes, KOCH's bacilli are capable of penetrating the epithelial defences, and,

in certain circumstances, of finding their way into the system. When swallowed with saliva or food, only a very small number of them penetrate the mucous membrane, and the great majority are excreted in the fæces; most of those organisms which pass through the mucous membrane are destroyed by the lymphatic glands.

Penetration may occur in the upper part of the digestive tract, even through the mucous membrane of the mouth, and COOKE, of Chicago, demonstrated the part played by dental caries in the ætiology of tuberculosis of the cervical glands. The small intestine, however, seems to be the part of the alimentary tract most vulnerable to the organism, especially during the digestion of fats.

Most of the bacilli reaching the stomach are destroyed by the gastric juice; in fact, according to KOCH, the vegetative form of the bacillus cannot withstand the action of the gastric juice, whereas the spore maintains its vitality when exposed to the same secretion. The organisms are conveyed through the intestinal wall into the lacteals by the phagocytes; still enclosed in the protoplasm of these leucocytes they are carried in the lymph, according to SCHALTDRUSEN, as far as the first set of lymphatic glands which oppose their progress. Once they have succeeded in traversing these glands, the bacilli, enclosed in the phagocytes, reach the cavernous sinuses of the mesenteric lymph glands which drain the part of the intestine through which they entered. The lymph flow at this point is retarded by the endothelial septa of the gland, and the infected phagocytes will usually be arrested. According to QUAIN the network of lacteals and lymph vessels in the mesentery in man passes through 130 to 150 glands varying in size from the dimensions of a millet seed to those of an olive.

What, then, becomes of the bacilli? Are they destroyed, and if so, how? Why should they, in some cases, form the starting point of a progressive infection of one sort or another? The phagocyte, the agency

by which the bacillus was able to penetrate the intestinal wall, is endowed with marked digestive powers, as far as bacteria in general are concerned, and can assimilate precipitates and insoluble particles of various kinds, which it may encounter in its passage through the tissues and circulation; but the acid-fast tubercle bacillus, protected by its waxy envelope, withstands the protoplasmic ferments and offers an efficient resistance to the destructive powers of the phagocyte.

It is generally believed that tubercle bacilli may even multiply while enclosed in a phagocyte, though this has not been proved; in theory, the phagocytic cytoplasm would appear to offer an unfavourable environment for the multiplication of bacteria since its purpose is to destroy them. It seems rather far-fetched to suppose that the tubercle bacillus actually thrives under conditions which are destructive to most bacteria.

The antagonism between the phagocyte and the bacillus can have only one of two results: either the phagocyte will die because it has ingested several bacilli or because the bacilli are sufficiently virulent to destroy it, or it will survive.

(1) If the phagocyte dies in a lymphatic gland the released tubercle bacilli will be deposited in the gland; here they may be destroyed in their turn because the environment is unfavourable, or they may survive and give rise to characteristic tuberculous lesions. The endothelial reaction induced will lead to the formation of giant cells and the usual pathological phenomena of tuberculosis in a lymphatic gland. In this way the bacillus leaves its stigma in the gland nearest the portal of entry, according to Conheim's law. Later on, the softening and caseation of the initial tubercle allows the bacilli to diffuse into the lymph stream and to form fresh lesions in lymphatic glands in the vicinity; in other cases the lymph stream may carry bacilli into the thoracic duct or the left duct, whence they will be poured into the bloodstream and disseminated throughout the body.

Frequently the organisms in the blood-stream will be deposited in the lung, because the capillary network at this site plays the part of a filter. This, in fact, explains the great frequency with which pulmonary lesions develop.

(2) It sometimes happens that only a few bacilli of moderate virulence penetrate the mucous membrane, and that these are tolerated for a time by the phagocytes which enclose them. The bacilli are then carried round in the circulation until the phagocyte dies, which may occur in some site distant from the point of entry. In this way lesions may arise in the most diverse regions : in the lungs, serous cavities, glands, skin or bones ; but there is always a predominance of pulmonary lesions for the reasons explained above.

In these cases no trace will be found of the fact that the bacillus gained ingress from the alimentary tract. Consequently Conheim's law cannot be accepted as having the general application which has been ascribed to it.

When the infected leucocyte preserves its vitality it is possible, and even probable, that the body will be able to get rid of the bacilli by a process commonly used to expel insoluble particles which are resistant to protoplasmic digestion. The phagocytes ingest such particles and, having passed through the intestinal mucosa by diapedesis, expel them into the intestine ; I can see no reason why the same process should not occur with Koch's bacilli.

On the other hand, an isolated organism which is carried through the blood and lymph capillaries until the phagocyte enclosing it dies, will be deposited at the point at which the dead leucocyte is arrested and form a capillary embolus. Bacilli so deposited very likely remain at that site for months or years until, for some unknown reason, they begin to proliferate ; but they may equally well lose their vitality and become innocuous.

There is, however, another mode of infection which I believe to be the usual one in the transmission of tuberculosis, namely, the passage of the filterable

virus from a tuberculous mother to her child. I will deal with this subject more fully when discussing heredity, as it more properly belongs there.

Differences in the Process of Infection and in the Transmission of Tubercle Bacilli according to Age.

I shall show later (pp. 105-112) that the intestinal mucosa of infants, which at birth lacks the complete development found in adults, is readily penetrable by micro-organisms (see figs. 13, 14, 15, 16, 17, 18 and 19), and this accounts for the extreme susceptibility of new-born infants to tuberculosis. But there is another mechanism, varying with the age of the subject, which plays an important part in relation to infection and the penetration of the tissues by organisms, and which influences the type of the disease seen at different ages. I refer to the differences of structure observed in the lymphatic system. In young subjects the glands are composed of lymphoid cords closely packed together; near the hilum the lymph sinuses are reduced in size and crowded with lymphatic cells, so that a filter, which is well-nigh impassable, is opposed to the progress of the bacillus.

In adults, on the other hand, the lymph cords are less closely packed, the lymph sinuses are larger and their loose trabeculæ form channels which are readily traversed by micro-organisms. Figs. 7, 8, 9 and 10 illustrate these differences of histological structure.

When discussing tuberculosis in negroes I showed that, as a result of repeated intestinal infections of various kinds and of the inflammatory reactions which affect the intestinal mucosa at intervals during life, micro-organisms from the alimentary canal may be able to penetrate the first line of defence offered by the mucous membrane. Having entered the lacteals they encounter the second line of defence, namely, the mesenteric glands, in which they are

deposited and eventually destroyed by the inflammatory reaction ; this process, however, does not leave the structure of the gland unaffected ; as in all prolonged inflammatory reactions, fibrous tissue is formed, and the gland becomes sclerosed. As age advances this sclerosis becomes more marked, since



FIG. 7.—Mesenteric gland from a young subject, showing the compact structure which offers a defence against micro-organisms.
Magnification : 100 diam.

the frequency and duration of intestinal troubles tend to increase, in most people, from year to year. Few escape this process, so that after a certain age the defensive mechanism of the mesenteric gland becomes more and more permeable.

Figs. 11 and 12 show sections of a mesenteric gland taken from a woman aged 35, who died of heart disease, and similar sections of a gland taken from a man of 56, who died following an accident; they show fibrosis of the gland with large lacunæ, offering

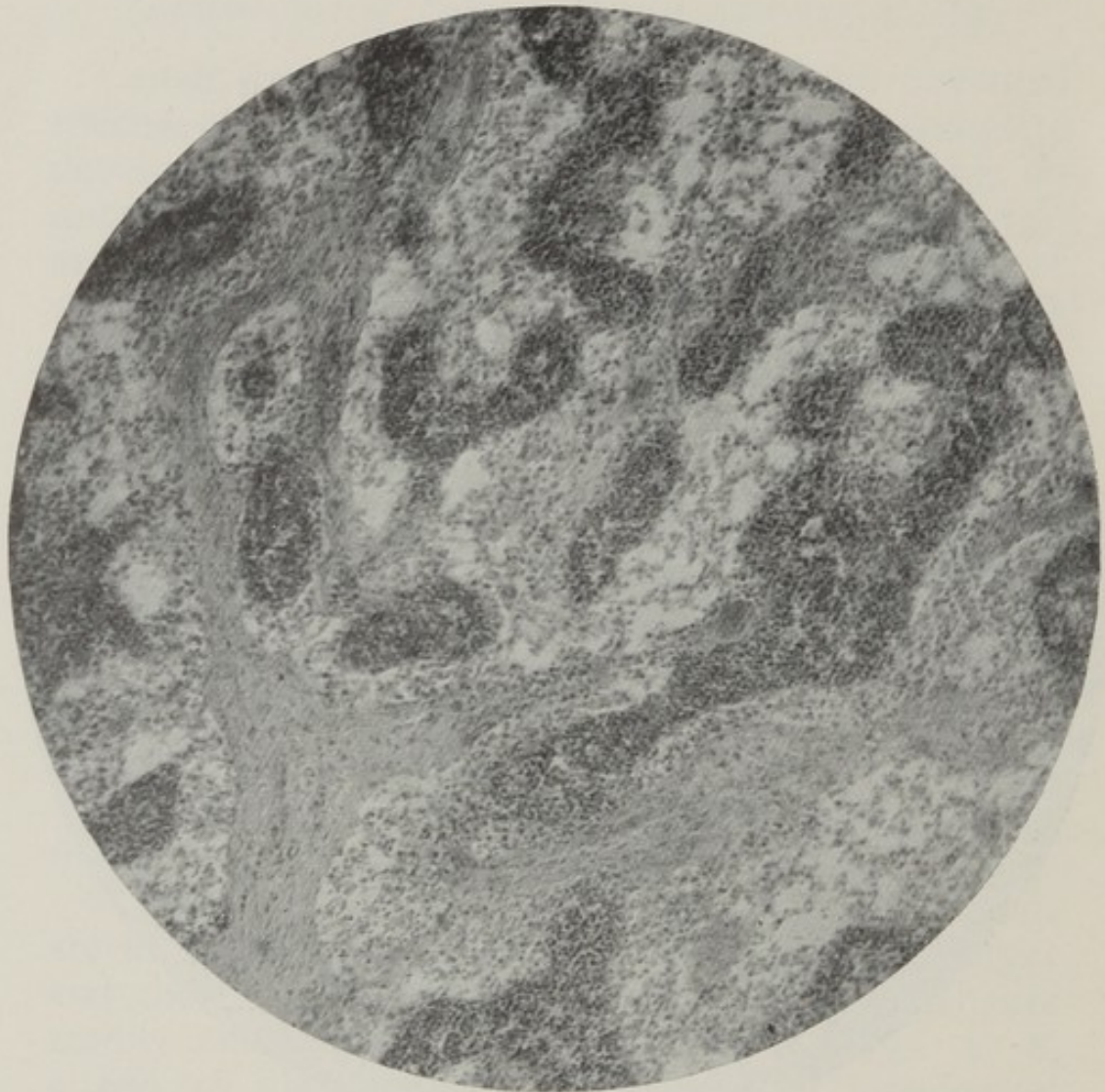


FIG. 8.—Mesenteric gland from an adult showing the lacunæ through which micro-organisms can readily pass.
Magnification : 100 diam.

a clear passage to micro-organisms, between the strands of fibrous tissue.

In the light of the foregoing discussion, let us try to decide what will happen to the bacillus, according to the age of the subject, when intestinal infection occurs.

(a) If the subject is an infant any bacilli penetrating the intestinal mucosa will reach the lacteals and be carried to a lymphatic gland where its progress will be arrested; it will not reach the lungs or other organs, or give rise to consumption, but will either

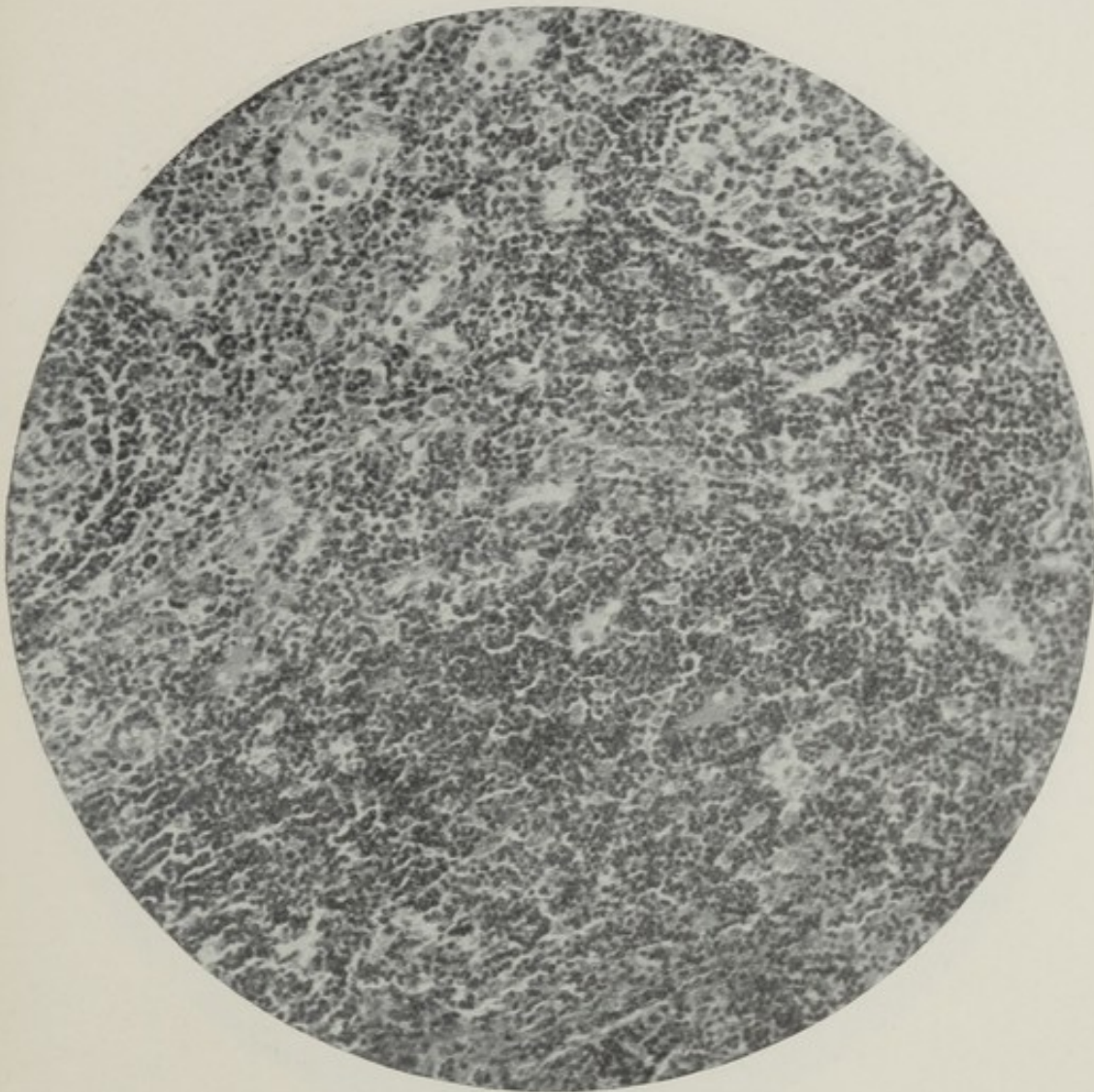


FIG. 9.—Mesenteric gland from a young subject; the tissues form a close-meshed filter.

Magnification : 150 diam.

be destroyed in the gland, or else will multiply and give rise to a primary lesion near the portal of entry, thus fulfilling Conheim's law. WEIGERT noted that during the early years the lymphatic glands provide an almost perfect filter.

CALMETTE, in a series of telling experiments in

which young kids were suckled by dams with tuberculosis of the udder found tuberculosis of the mesenteric glands in all the young animals.

When the infant is infected in this way, during the first few months after birth, the glandular lesions

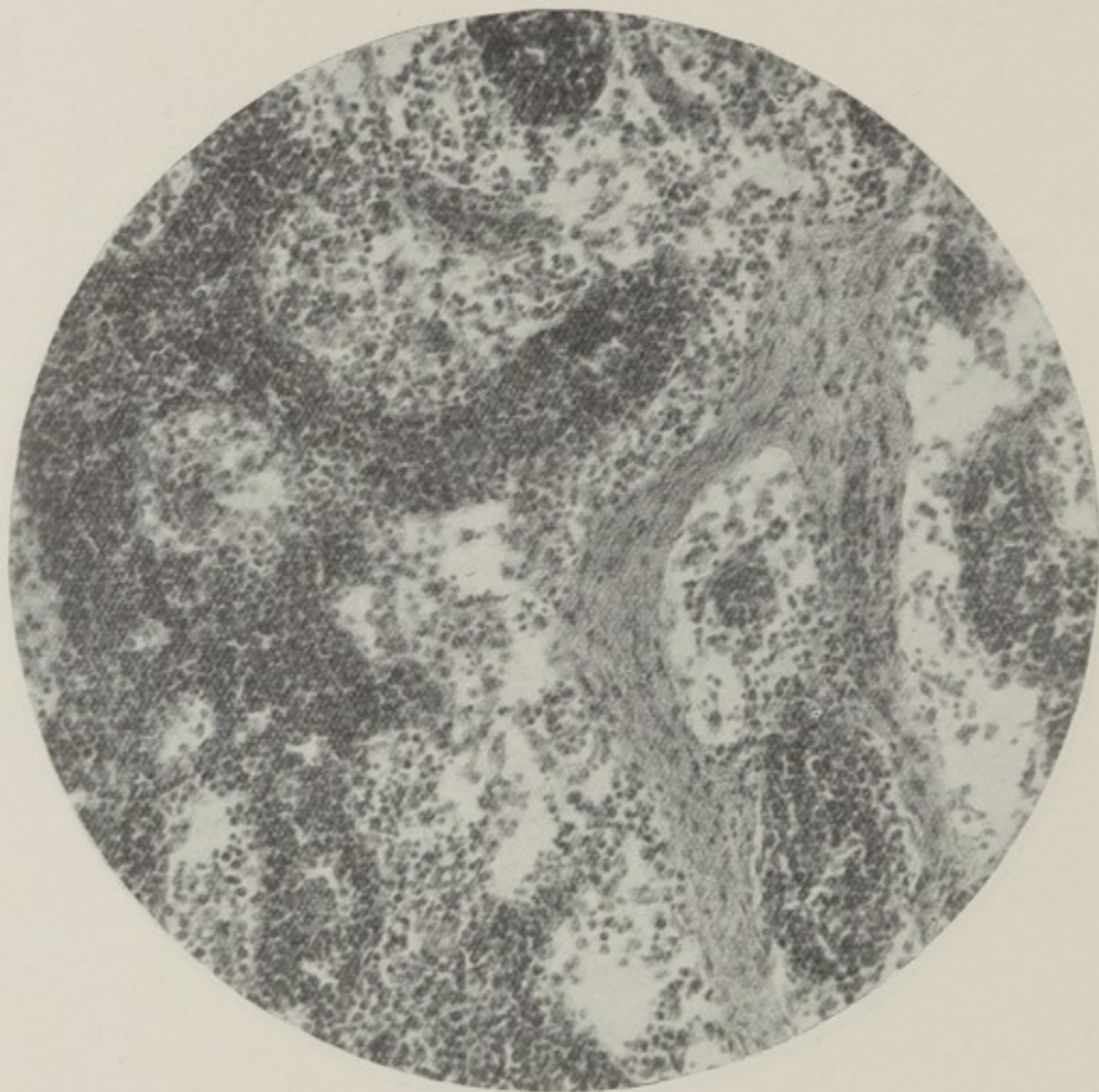


FIG. 10.—Mesenteric gland from an adult, showing lacunæ and fibrous tissue.

Magnification : 150 diam.

appear to spread gradually ; tuberculous peritonitis or enlargement of the mediastinal glands may follow or meningitis, the common form of tuberculosis in infants infected at this early age. In this connection it is worth while recalling the case of the Neuenburg midwife whose 11 victims, infected at the time of

birth, succumbed within fourteen months ; we may also recall the high incidence of meningitis among infants breast-fed by a mother with advanced tuberculosis.

Certainly this type of infection, starting in the mesenteric gland nearest the portal of entry, is not

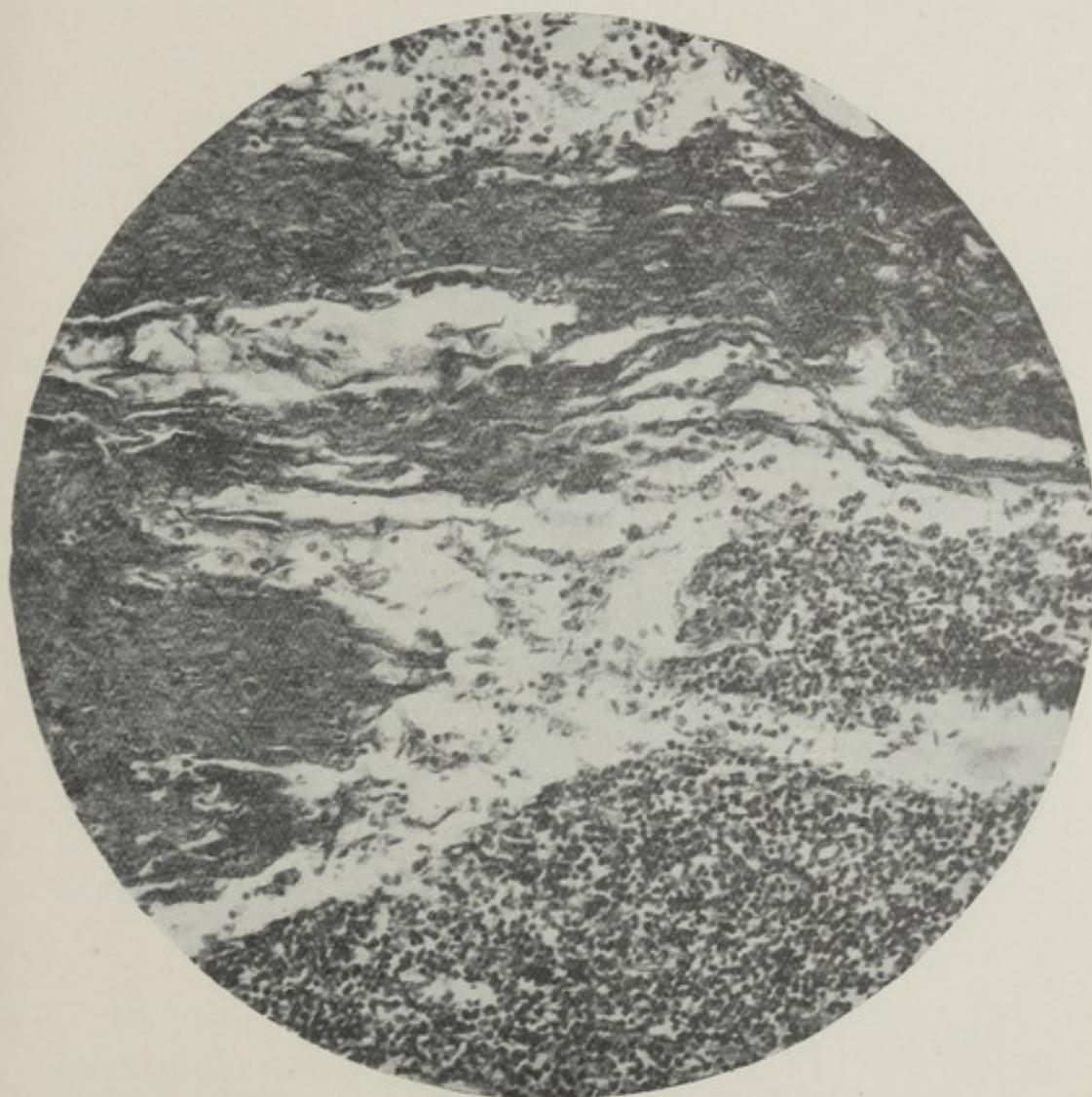


FIG. 11.—Mesenteric gland from a woman aged 35, who died of heart disease. Fibrosis, with the formation of spacious lacunæ through which micro-organisms can readily pass.
Magnification : 150 diam.

unique. The bacillus is capable of penetrating the mucous membrane of the intestinal tract at any point, especially where the mucosa is incomplete.

(b) In adults, where the mucosa is fully developed,

the tubercle bacillus may still be able to penetrate the intestinal wall even where the mucosa is perfectly sound, as CHAUVEAU, and subsequently DABROKLOWSKI were able to show ; this is contrary to the opinion of KOCH and BAUMGARTEN, who asserted that the bacillus always left signs of its passage.



FIG. 12.—Mesenteric gland from a man, aged 56, who was killed accidentally. Multiple lacunæ situated in the interstices of abundant fibrous tissue. The gland is little more than a sieve.
Magnification : 100 diam.

Whatever the origin of a primary local lesion may be, the permeability of the lymphatic glands in the adult leaves the way clear for the infecting organism to pass on into the lymph stream, so that CONHEIM'S

law no longer holds ; the organisms pass from the lymphatic system to the heart and are disseminated by the blood-stream. Leucocytes enclosing living bacilli may, in these circumstances, be arrested and release the bacilli in any organ of the body, or at any point accessible to a migratory cell.

The commonest site of arrest, however, is the lung, owing to its fine capillary network. Solid particles of all kinds circulating in the blood, whether bacterial in nature or not, will be most readily deposited here. It is in the lungs that circulating carbon particles are arrested and give rise to pulmonary anthracosis, as JOUSSET and CALMETTE showed, by giving Indian ink to animals by mouth. This classical experiment, confirmed by VANSTEENBERGH and GRYSEZ, has also been performed with powdered carmine. It has also been shown that if the œsophagus of a rabbit is ligatured and the animal is then allowed to inhale lamp-black, anthracosis will never occur. The lungs arrest bacilli which have reached the blood-stream from the intestinal canal in the same way as they arrest carbon particles, and this, no doubt, is one reason why pulmonary tuberculosis is the commonest form of the disease after a certain age. In my view, however, there is another and more important reason, which I will discuss after dealing with the question of hereditary transmission of the filterable virus.

* * * * *

To sum up, though infection through the gastrointestinal tract occurs, it is rare in adults. Under the usual conditions of modern life the numbers of tubercle bacilli ingested are small and most of them are destroyed by the digestive juices or eliminated. In adults, moreover, the intestinal mucosa, though permeable to some extent by organisms, offers an important obstacle to their penetration into the system ; the majority of bacilli, therefore, do not penetrate the mucosa, while those which succeed in doing so may be destroyed by the lymphatic glands

or, after being carried round by a leucocyte in the blood-stream, may be returned to the intestinal tract by diapedesis.

I still await formal and conclusive clinical examples of infection by way of the alimentary tract in adults.

In new-born infants the position is different; the intestinal mucosa is much more permeable, and incontrovertible cases of infection by this route have been put on record. We are, however, ignorant of the share which this mode of infection plays in the general dissemination of tuberculosis.

D. *Infection between Animals.*

Transmission of tuberculosis from one animal to another also seems to be decidedly rare, if it occurs at all, under the usual conditions of life and apart from special cases. Even when the environment is particularly favourable to the spread of the disease—for example, when animals are infected experimentally, in various ways, with massive doses of highly-virulent material—transmission of the disease from inoculated animals to others sharing the same quarters does not occur in the great majority of cases.

REMLINGER's experiments demonstrate this conclusively. His tests were carried out not only on normal guinea-pigs, which are extremely susceptible to experimental inoculation, but also upon animals previously sensitised with intraperitoneal injections of killed tubercle bacilli. His conclusions were as follows :—

“Sensitised guinea-pigs do not acquire tuberculosis more readily than non-sensitised control animals; whatever the explanation of this observation may be, the bacteriological paradox to which I have drawn attention is evident, namely, the marked susceptibility of guinea-pigs to various forms of experimental tuberculosis, and the extreme rarity of infection occurring between these animals in laboratories and breeding establishments.”

There are, however, some animals susceptible to

tuberculosis between which infection appears to occur : this is the case with cattle, and Prof. CALMETTE brings this fact forward as a proof that infection occurs in man, in his reply to the inquiry set up by *La Vie Medicale*. The chief line of reasoning is as follows :—

Although it is not stated, it is understood—since otherwise the experiment would be purposeless—that the conclusions drawn from cattle can be taken to hold good for man. Once this premiss has been laid down, “an experiment can be performed with a cow suffering from advanced pulmonary tuberculosis, and coughing up tubercle bacilli and excreting them in the fæces upon the straw of the byre. If this cow dies, it can be replaced by another one with open tuberculous lesions. All, or nearly all, of a series of 20 young cows brought into contact with the sick animal will, at the end of a year or eighteen months, react to the tuberculin test, and when examined after being slaughtered, will show the usual range of tuberculous lesions. Therefore,” Prof. CALMETTE concludes, “these young cows are infected by living in close association with a single tuberculous animal.”

Let me point out, in the first place, that there is no formal assurance that the young animals brought into contact with the tuberculous cow were free from a tuberculous heredity. The absence of a tuberculin reaction at the outset is by no means a proof of this : subjects carrying the filterable virus or the organisms in a saprophytic form may offer no allergic manifestations for some time, but are tuberculous none the less. Tuberculosis being common among cattle the number of young cows with a tuberculous heredity must be considerable, and in these the disease will remain unsuspected as it does in infants. Signs of it do not appear because the animal is slaughtered too young. In order to make the experiment under consideration conclusive, control experiments would have to be conducted under exactly similar conditions, the only variant being the infecting animal itself.

But let us suppose that the experiment is sound :

is it really convincing as regards human infection? The conditions of infection are utterly and essentially different in the two cases; the human subject does not expectorate or defæcate bacilli into his surroundings, or wallow in excrement; nor does he lick himself and his companions; he does not live in the mud and filth of a stable; he keeps himself clean, and does not feed on more or less grimy raw food, or stay out for days at a time in the rain.

In fact all the factors which favour infection are those which are not common to men and cattle.

Can it be regarded as logical, then, to attempt to compare cattle with men in this respect? Besides, if similar experiments are performed with other animals, such as guinea-pigs, the findings are entirely different. Infection no longer occurs. If several guinea-pigs, one of which is suffering from advanced tuberculosis, are placed in the same cage, the tuberculous animal will never infect its fellows, although guinea-pigs are particularly susceptible to tuberculosis, whatever method is used to transmit it to them.

My opponents will promptly point out that infection fails to occur between guinea-pigs because these animals do not expectorate their sputum; but I may point out that guinea-pigs have frequently been kept on premises occupied by tuberculous patients who are coughing up enormous numbers of bacilli, and the animals have never become tuberculous.

Why should the case of tuberculosis in cattle be retained as an argument while the negative case of tuberculosis in guinea-pigs is dismissed? Neither is applicable to man—neither the negative example which supports my own view, nor the positive one which tends to disprove it. What is the value of an argument based on such questionable foundations?

* * * * *

It is only in the case of adults that I question the occurrence of infection under existing conditions of life. Nevertheless, Prof. CALMETTE raises the follow-

ing objection to my view : " Infection can be induced simply and quickly by feeding the new-born calf of a sound dam with the raw milk of a cow suffering from tuberculosis of the udder." I cannot see what this fact has to do with infection between adult men.

(1) The newly-born subject being liable to infection, as I shall show later, the example does not disprove my view but supports it.

(2) It has no reference, however, to infection in man, since adult human subjects are not in the habit of taking their nourishment directly from cows affected with tuberculosis of the udder, and of swallowing positive cultures of KOCH's bacilli in consequence.

(3) Even if we suppose that tuberculous cows' milk can infect adult mankind—a supposition which is so far unproven—this has no bearing on infection occurring between adult human subjects.

If the views I have expressed in this chapter are sound, they form a complete defence against the criticisms set out above, and such criticisms, therefore, cannot affect my opinion.

* * * * *

The foregoing discussion leads us to two main conclusions.

(1) Tuberculosis is hardly infectious at all to adults in good health.

(2) The occurrence of conjugal infection and infection in sanatoriums and hospitals has never been conclusively proved, and in any case must constitute only an exceptional method of transmission of the disease.

CHAPTER V.

INFECTION IN INFANTS AND THE NEWLY-BORN.

IN view of the scarcity of facts demonstrating the occurrence of infection in those adults who are in continual contact with tuberculous patients, many supporters of the theory of infection have felt bound to acknowledge that, in practice, the risk of infection for this class of subjects is small. But will they consent to change their views and return to the theory of heredity? On the contrary, they bolstered up their opinions by arguing that infection occurs early in infancy, and that the new-born child is the chief victim.

At the present moment the predominant theory of the transmission of tuberculosis is that a child born of tuberculous parents does not inherit either the disease or a tendency to acquire it, but contracts tuberculosis after birth from his parents. An observation has been quoted in support of this which is less speculative than the other arguments put forward on behalf of the theory of infection. REICH reports that 10 new-born infants, whose mothers had been attended in their confinements by a certain consumptive midwife in Neuenberg, all died of tuberculous meningitis within fourteen months, while no other deaths from this cause were recorded among infants in the same city whose mothers had been attended by other midwives. The tuberculous midwife was in the habit of performing mouth-to-mouth respiration with the infant, even when no signs of asphyxia were present.¹

There seems to be no reason to question this story, which has all the value of a laboratory experiment ;

¹ REICH. "Société Centrale de Médecine Veterinaire." October, 1922.

on the other hand, infants born of parents who are free from tuberculosis will sometimes die from meningitis, or develop local tuberculous lesions during the early years of life. Infection must, therefore, be accepted as occurring in new-born children, but two questions naturally arise out of this :—

(1) Why are infants susceptible while adults, for the most part, are resistant to infection?

(2) Is infection frequent at birth, and does it account for all the cases of tuberculosis in adults?

(1) The key to the susceptibility of the infant has been sought in the difference in structure of the intestinal mucosa in the infant and the adult. It is admitted, nowadays, that the bacillus enters the system as a rule through the digestive tract, and DISSE has shown that the epithelial cells of the intestine assume their final form only after the establishment of the digestive functions—that is to say, a few days after birth. The accompanying microphotographs (figs. 13, 14, 15, 16, 17, 18 and 19), show these structural differences according to age.

In my opinion, it is not only this structural difference in the intestinal mucosa which governs the susceptibility of the new-born child and the adult, but the fact that the lymphatic system is incompletely developed at the time of birth, and only later becomes a defensive mechanism, guarding the body against invasion by organisms present in the intestine. During the first week of life, then, the intestine is especially permeable ; not only organisms but the large molecules of toxins or antitoxins are able, in the early days of life, to find their way through the intestinal mucosa more readily than they do later.

BEHRING rightly laid emphasis on this argument in support of his theory of the infantile origin of tuberculosis. “No convincing example exists of the transmission of tuberculosis between adults,” he says. “Infection must take place in infancy, not by inhalation, but by ingestion of bacilli in the food. Tubercle bacilli, introduced into the intestine in tuberculous

milk, probably infect the lymphatic glands and then, in most cases, lies dormant until adult life is reached."

(2) Is infection frequent at birth, and does it account for all the cases of tuberculosis seen in adults? A superficial examination of the arguments already brought forward will not suffice to secure conviction

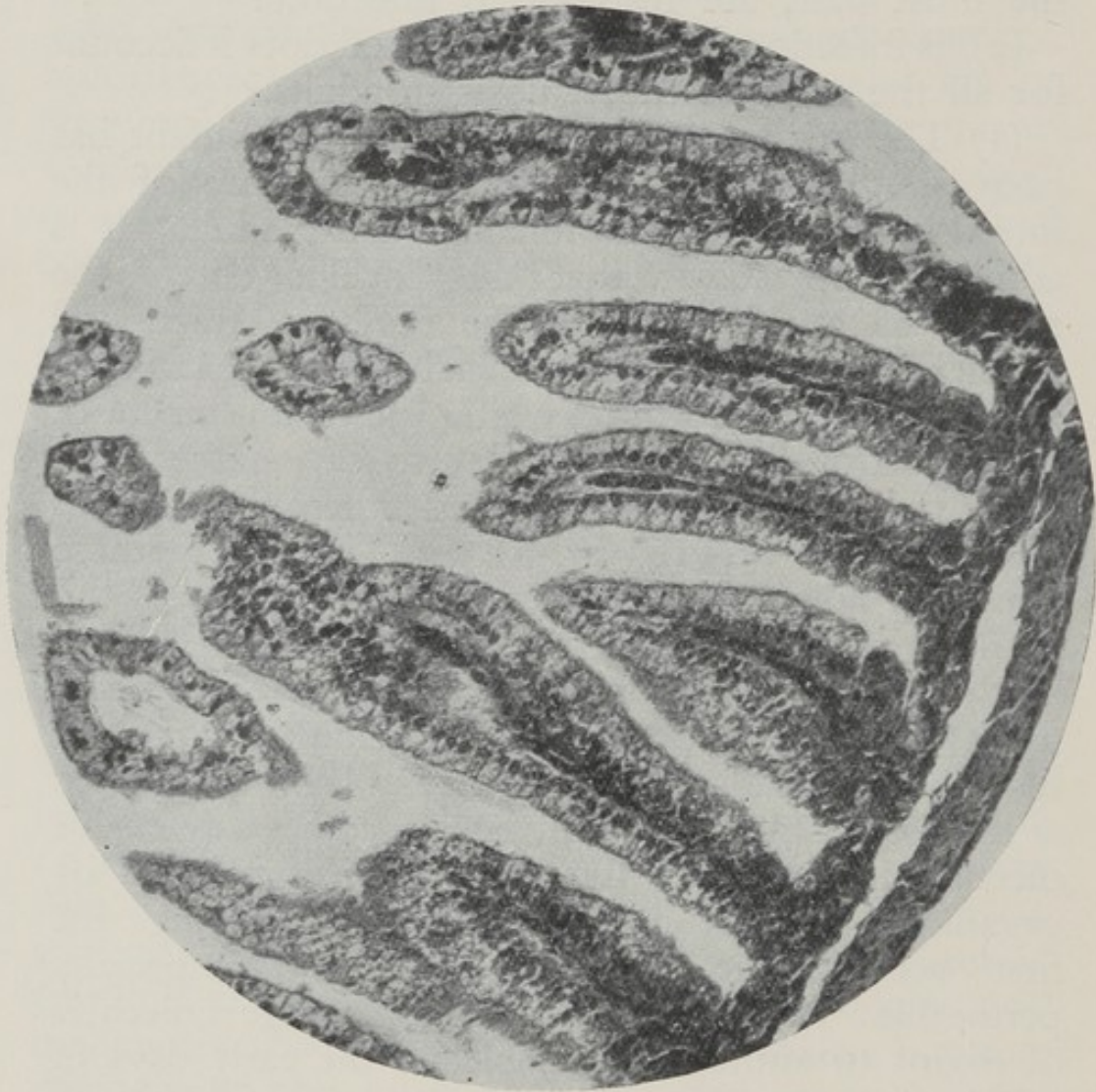


FIG. 13.—Small intestine of a guinea-pig at birth. Absence of lymphoid tissue. Permeability of the epithelial lining.
Magnification : 150 diam.

on this point. In the cases of undoubted infection occurring among infants the type of tuberculosis most frequently seen is a fatal meningitis; the case of the consumptive midwife quoted above goes to

show that infants infected at birth died of meningitis within a period of a little more than a year, at the outside.

Can we assert that cases of pulmonary tuberculosis in adults, which are numerically common, have their origin in an infection acquired in infancy, rather than

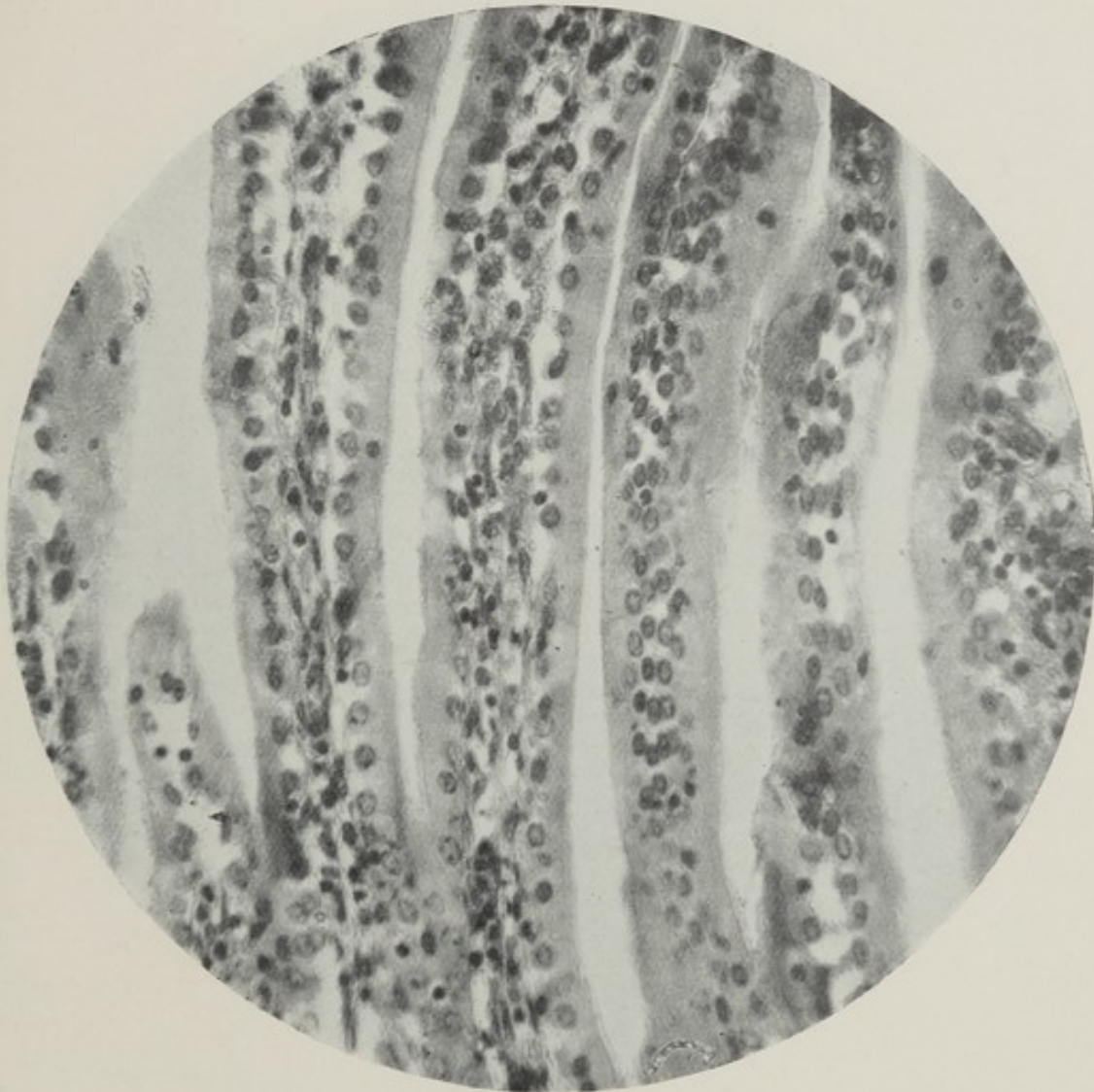


FIG. 14.—Small intestine of an adult guinea-pig, showing the epithelial and lymphoid defensive mechanism.
Magnification : 150 diam.

in the hereditary transmission of the disease or of a predisposition to it? I cannot think so, whatever the conventional view.

The chief argument put forward by authorities

on tuberculosis, in proof of the danger of infection during infancy, is drawn from statistics dealing with the children of tuberculous parents ; these statistics show what happens when, on the one hand, such children are left in the home environment, and when, on the other hand, they are segregated from their



FIG. 15.—Small intestine of a guinea-pig at birth.
Magnification : 275 diam.

tuberculous parents and placed in homes or nurseries, under special supervision, or entrusted to the care of welfare societies. In the second case mortality appears to be materially reduced. All other arguments, in the view of the supporters of the theory

of infection, fade into insignificance beside this finding.

The experiment is at present being made on a very large scale; those children may be reckoned by the thousand who, thanks to the devotion of many generous women and medical practitioners who are

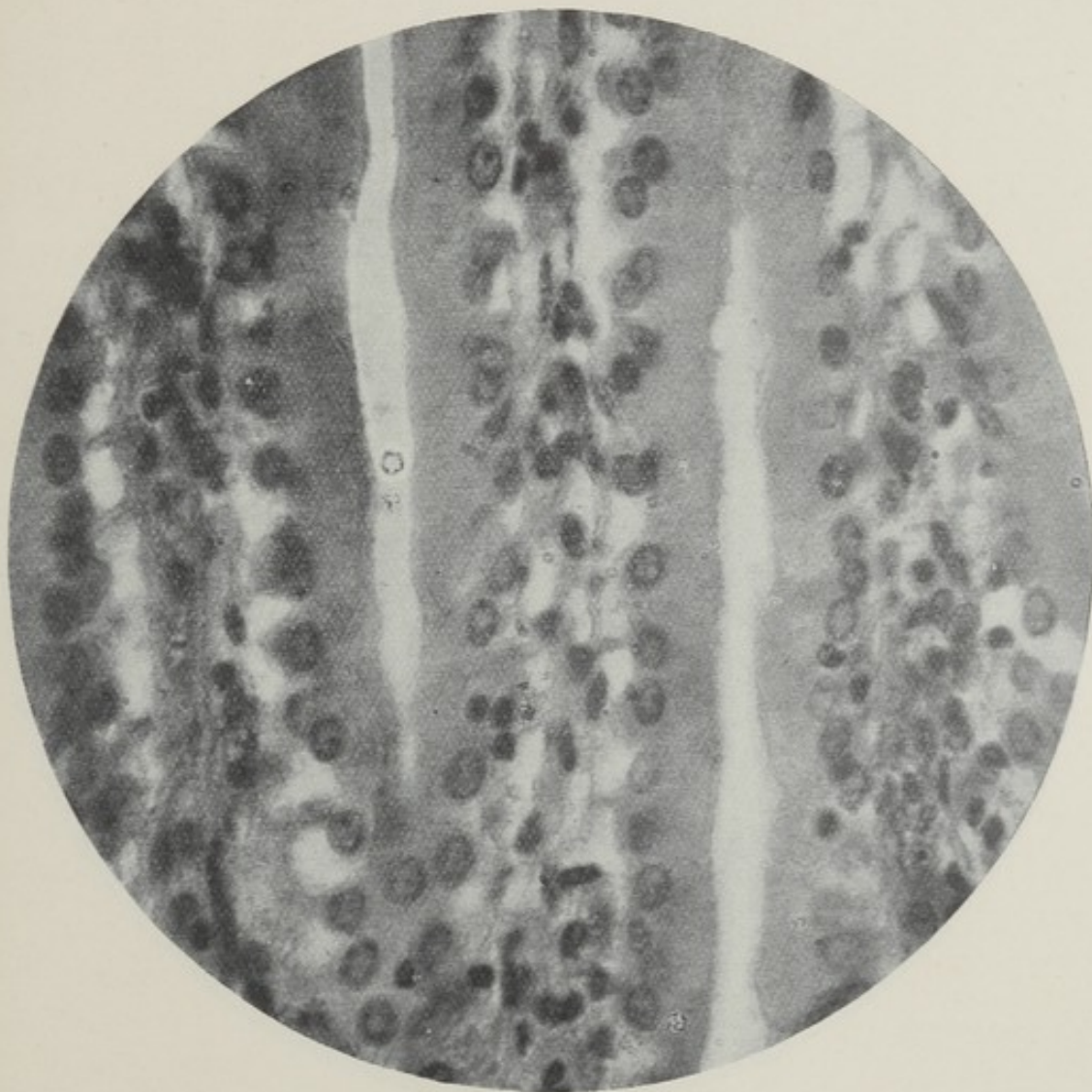


FIG. 16.—Small intestine of an adult guinea-pig.
Magnification : 275 diam.

interested in this work, are saved from death by these admirable societies which were first promoted by GRANCHER. The future welfare of the race depends, to some extent, on such activities, and it would be ungrateful to disparage them in any way. I wish

to emphasize, therefore, the fact that the remarks which follow must not be regarded as criticism, however mild, of work which deserves the warmest public gratitude.

Having paid this tribute, which is fully deserved, let me say that my sole purpose is to examine dis-



FIG. 17.—Duodenum of a full-term human fœtus. Lymphoid tissue scanty. Magnification : 100 diam.

passionately the conclusions which can be drawn from these extensive experiments with regard to tuberculous infection. I have no wish to be carried away by easy optimism, but it seems to me that these experiments have little value as a demonstration.

In any experiment it is essential that there should be a limited number of variable factors, otherwise it becomes impossible to assess the influence of each factor severally upon the results obtained. Failure to observe this rule has led to the drawing of inaccurate conclusions from statistics showing the mortality-



FIG. 18.—Duodenum of adult man. Abundant lymphoid tissue.
Magnification : 100 diam.

rate among new-born children entrusted to welfare societies.

When the infants were removed from contact with their tuberculous parents they were placed at once in hygienic surroundings under careful medical

supervision, and given appropriate feeding, all of which must have helped to save a number of them from death.

Undoubtedly the guardians acted wisely in giving these children the benefit of all the advantages of modern infant care, and it would be difficult to explain



FIG. 19.—Small intestine of adult man. Section showing the importance of the defensive lymphoid tissue.
Magnification : 150 diam.

to them why, in the interests of scientific research, the child should have been denied these advantages of modern infant care, and each experiment confined to the study of a single variable factor. But it cannot

be pretended that it was only by removing the infant from the danger of infection in his home that such successful results were obtained; and I propose to show that the essential factor in the reduction of mortality is of quite a different order.

First, let us consider the general causes of infant mortality during the first year of life. These causes are set out below in a table taken from the *Rapports du Service de la Statistique du Comité National de Défense contre la Tuberculose* (1925).

PRINCIPAL CAUSES OF DEATHS OF INFANTS UNDER ONE YEAR,
REGISTERED IN FRANCE IN 1925.

Cause of death	Males	Females	Total
Congenital debility and defect	7,239	5,847	13,086
Diarrhœa and enteritis	6,458	4,964	11,422
Respiratory diseases, excluding phthisis	4,098	3,147	7,245
Simple meningitis	1,652	1,341	2,993
Acute bronchitis	891	701	1,592
Whooping cough	573	631	1,204
Tuberculosis (all forms)	579	458	1,037
Measles	401	366	767
Influenza	434	324	758
Acute enteritis	106	77	183
Violent death	214	156	370
Other diseases	3,362	2,315	5,677
Total deaths from known causes	26,007	20,327	46,334
Unknown or indefinite diseases	11,140	8,134	19,274
Total of deaths under one year	37,147	28,461	65,608

Out of a series of 65,608 deaths of infants under one year old in the whole of France in 1925, the cause of death was not stated in 19,274. There remain, therefore, 46,334 deaths from known causes, of which only 1,037 were due to tuberculosis (2·34 per cent. of the total deaths). It is clear, then, that the mortality rate from tuberculosis, in children under one year of age, according to official figures, must be extremely low as compared with other causes such as infantile diarrhœa, enteritis and acute respiratory conditions. Such a small proportion of deaths from tuberculosis does not seem to be in keeping with the known facts,

and there can be no doubt that a certain number of the cases classed under simple meningitis were in reality cases of tuberculous meningitis, while certain bronchial, pulmonary and intestinal conditions doubtless had a tuberculous origin; so that we should probably obtain a figure nearer the mark if we doubled or even trebled the official figure.

Indeed, in hospitals where the cause of death can be confirmed by post-mortem examination, the percentage of deaths from tuberculosis is found to be higher still; but we cannot use hospital figures as a basis for argument since the death-rate among patients in a hospital applies only to a selected group of persons, and does not correspond to that of the general population outside. Moreover, therapeutics and hygiene alike have little effect in the treatment of tuberculous infants, whereas they are the means, in hospital, of saving the lives of numbers of children suffering from other conditions, who would inevitably die if left in their own homes; consequently, deaths from tuberculosis among infants in hospital form an unduly large percentage of the total deaths. According to statistics furnished by the child welfare societies in my own district, out of 1,007 deaths of infants under one year of age occurring in 1928, only 11 deaths from tuberculosis (1.08 per cent.) were registered. These figures apply to infants segregated from their parents, living under special conditions and supervision; for the purposes of this discussion, we must pay no more attention to this unduly low figure than to the unduly high one found in hospitals.

It seems probable that 5 per cent., instead of 2.34 per cent as given by the *Service de la Statistique*, may be taken as an average figure for the infantile mortality-rate from tuberculosis, and used as a basis for further argument.

If, then, all the deaths from tuberculosis in infants under a year could be prevented by placing them under special conditions, the mortality rate would not be reduced by more than 5 per cent. Now the

child welfare societies, or at any rate some of them, issue statistics showing a decrease in infant mortality which may reach, or even exceed, 30 per cent. in infants reared under modern methods of child management. So that the excellent results obtained by these methods owe very little to the mere prevention of infection.

The saving of infant life accomplished by these societies is due, almost entirely, to the carefully-thought-out technique used in feeding infants, which reduces enormously the number of deaths from gastro-enteritis and infantile diarrhoea. The fact that the mortality rate decreases substantially among infants segregated from their tuberculous parents cannot, therefore, be used as an argument in support of the theory of infection; it is not merely because these children are removed from an infected environment that they survive, but because they enjoy care based on hygienic principles, particularly in regard to feeding, so that one of the chief dangers of early infancy is minimised.

Indeed, the same reduction in the mortality rate has been found among children, born of parents who are free from tuberculosis, when they are placed under similar sanitary conditions and given the same careful supervision. Between the years 1860 and 1900, the infantile mortality-rate for the whole of France averaged about 17 per cent. Thanks to the sanitary measures advocated for the last quarter of a century, that percentage had fallen, in 1926, to round about 10. This rate is again reduced substantially when infants who are left in their home environment are carefully supervised by health visitors. The Franco-American Foundation in the Lyons region, for instance, has succeeded in reducing the death-rate from diseases of early infancy by more than two-thirds; this figure applies to infants born within the city who are under the care of the Foundation, and includes indiscriminately those born both of tuberculous parents and parents free from tuberculosis.

Thanks to this welfare work, statistics show that

for the last nine years, among 88,470 "supervised" infants the total number of deaths during the first year of life was only 3,107 (3.51 per cent.). Such remarkable success, which is summarized in the accompanying table, does not depend merely on the prevention of infection, since the great majority of the infants included in the statistics were born of parents who were free from tuberculosis, and since many of those born of tuberculous stock were left in the care of their family.

In the Lyons creches, where infants are brought in the morning by their mothers, and taken away again in the evening, similar good results are obtained.

STATISTICS SHOWING THE MORTALITY RATE AMONG INFANTS UNDER ONE YEAR OF AGE, VISITED BY THE FRANCO-AMERICAN FOUNDATION IN LYONS.

Years	No. of Infants		Deaths		Per cent.
1920	..	8,960	..	308	3.43
1921	..	9,916	..	438	4.41
1922	..	10,255	..	337	3.28
1923	..	9,231	..	295	3.01
1924	..	9,312	..	336	3.60
1925	..	9,846	..	301	3.05
1926	..	10,477	..	384	3.66
1927	..	10,599	..	346	3.26
1928	..	9,874	..	362	3.66
Total	..	88,470		3,107	3.51

STATISTICS OF DEATHS IN THE LYONS' CRECHES.

Years	No. of Infants		Deaths		Per cent.
1924	..	579	..	22	3.8
1925	..	549	..	19	3.46
1926	..	577	..	26	4.55
1927	..	537	..	18	3.35
Total	..	2,242		85	3.78

On the other hand, the mortality is much higher among foster-children who are separated from their parents and put out to nurse by the Assistance Publique in homes in the country, where they are not closely supervised, and where feeding is often unsatisfactory. Although these infants are placed in the care of foster-

parents who are free from tuberculosis—which amounts to saying that they are out of reach of infection—the death-rate among them is high and shows no sign of diminishing substantially.

The following table gives the death-rate during the first year of life among foster-children under the Assistance Publique for the last twenty years :—

Years	Death-rate Per cent.	Years	Death-rate Per cent.
1908	22.19	1919	38.47
1909	16.34	1920	51.39
1910	13.90	1921	36.88
1911	24.76	1922	18.43
1912	15.15	1923	28.34
1913	20.84	1924	19.33
1914	19.61	1925	18.94
1915	10.61	1926	20.30
1916	33.17	1927	21.28
1917	35.72	1928	25.18
1918	49.16		

Almost all such foster-children were breast-fed before 1914; at the present time they are seldom given to wet-nurses, and artificial feeding is the rule.

Let me hasten to add that, although the arguments of statisticians interested in child welfare cannot be regarded as demonstrating the importance of infection, the demographical documents on which such arguments are based contain no convincing evidence to the contrary, and cannot be said to disprove the idea of the transmission of infection after birth.

As a matter of fact, whether the infant is held to be tuberculous at birth, or to have become infected during the first weeks or months of life, the disease will only manifest itself, as a rule, at the end of adolescence or the beginning of adult life.

Signs of latent infection will only appear in most cases between 20 to 30 years of age. In order to ascertain the value of the segregation of infants as a method of prophylaxis the incidence of the disease must be investigated, in the segregated persons, between the ages of 20 and 30 and between those ages only.

Such an investigation is of importance, and will take some time to carry out, but it is perfectly simple ; it should be undertaken without delay and pursued systematically for a quarter of a century. This is a task for our successors.

They will have to select a number of infants who have been removed from tuberculous parents at birth, and then determine the death-rate in the series between the ages of 20 and 30 years. If the subjects chosen do not die of tuberculosis during that period the value of segregation as a prophylactic measure will have been demonstrated ; if, on the contrary, they die at the same rate as subjects who were not segregated, the measure will have been shown to be valueless.

As long as such an investigation has not been carried out, under appropriate scientific safeguards, it will be impossible to assess the value of a measure which consists in the removal of the infant at birth from the tuberculous environment into which it is born. Until that is done we can only regard a few infants who develop rapidly-progressive tuberculosis as true cases of infection occurring after birth. It seems, in point of fact, as though infants under such conditions do develop rapidly-progressive forms of the disease, such as meningitis or, more rarely, caseous pneumonia or tuberculous peritonitis. Generally they die within a year of infection.

This does not mean, however, that all infants who die from tuberculosis during the early months of life must have been infected after birth.

There is nothing to prove that infection during infancy is the source of the disease in the innumerable forms in which it attacks adolescents and adults, especially those between 20 and 25 years of age.

CHAPTER VI.

HEREDITY.

Discussion of Clinical and Demographical Arguments Relating to Tuberculous Heredity.

(1) *Definition.*

Prof. LEON BERNARD, in his address attacking the theory of hereditary tuberculosis, published by the *Presse Medicale* in 1928¹, offered as a conclusive argument the fact that the theory of heredity clashes with the principal biological laws which govern heredity under other conditions. "Heredity," he wrote, "is a fixed and not a variable factor. If this fundamental axiom is accepted, how can it be supposed that an organism, by means of the pathological accident which the tuberculous infection of an individual in a family represents, could be influenced in so profound and permanent manner as to be transformed in nature and function? Modifications in the tissues developing as a result of infection could not become a final, heritable quality in the offspring of the patient."

That is true; the main characteristics of a species cannot be modified by a change in environment, or by any external influence, whether infective or of some other nature, which temporarily disturbs the vital functions of the subject. We have sure proof of this in the persistence of the various animal species through countless ages; in spite of tremendous upheavals they have remained unchanged in form and function. The *lingula* to-day shows the same

¹ LÉON BERNARD. "Tuberculose et Hérité." *Presse Médicale*, March 24, 1928, p. 371.

characteristics which it possessed in the remote past ; among the innumerable creatures which once lived in the Cambrian seas, a certain number showed morphological characteristics which have been perpetuated down to the present day ; fossils of plants of the primary period bear a striking resemblance to certain modern plants. Examples of organisms which have maintained their form unchanged through incalculable centuries are numerous.

Tuberculosis is not calculated to disturb the principle of preservation of the species, or to alter the structure of the embryonic cell or the fundamental properties of its chromosomes. The cell is immutable, and cellular heredity—that is to say, true heredity—cannot be influenced by tuberculosis.

But the cell, though it displays this permanence of structure, does not constitute the whole organism ; the higher animals are supplied also with tissue fluids which, although they cannot affect the cell architecture, do exert an action on certain of the functions of the organism. Changes of varying importance and duration may occur in these fluids, and are the basis of many pathological conditions, some of which are transmissible, to a certain extent, from parents to their offspring.

The tendency of the tissue fluids to agglutinate or precipitate certain substances is frequently hereditary ; the serum reactions of a mother are often found to be identical with the serum reactions of her children.

RIBADEAU-DUMAS, CUEL and PRIEUR proved that a positive complement reaction in a tuberculous mother at the termination of pregnancy is associated with a positive reaction in the child, although it appears to be sound at birth. In such cases there is certainly transmission of an acquired reaction from the tissue fluids of the mother to those of the fœtus. Certain organisms are transmitted in the same way. It would be puerile to refer to hereditary syphilis, but for the fact that I wish to make it clear that the term “heredity” has widely different meanings ;

the hereditary infection in syphilis does not modify the fixed characteristics of the species in any way, yet the hereditary factor cannot be denied.

The heredity we are discussing, however, is quite different ; the effects are only temporary, and influence only the functions of the individual, leaving the fundamental properties of the cell unchanged. To argue that the principle of immutability of the species precludes the inheritance of tuberculosis is equivalent to denying the existence of hereditary syphilis on the same grounds.

The argument depends on confusion in the definition of the term "heredity," which has several meanings and is applied to several distinct hereditary phenomena, some of which are permanent and unchangeable, and others variable and impermanent ; the phenomena in the first group include the characteristics of cell structure, those in the second group include the properties, composition and stability of the tissue fluids, and at times, no doubt, some of the secondary and provisional characteristics of the cells. In order to clear up the terminology applying to this point it seems wise to give a definite name to this phenomenon of transmission independent of changes in cell structure ; the term *paraheredity* seems to me to be suitable.

* * * * *

These preliminary considerations having been set out, let us consider the clinical and demographical arguments which may be applied to tuberculous heredity. For this purpose I shall attempt to answer the two following questions :—

(1) Does clinical medicine provide any facts which demonstrate the hereditary transmission of tuberculosis ?

(2) Out of 100 tuberculous patients what proportion will come of tuberculous stock ? And how is it that in the enormous literature associated with tuberculosis it has proved impossible to find the answer to this important question ?

(2) *Clinical Facts connected with Heredity and the New-born Child.*A. *Fætal Tuberculosis.*

Among examples of the congenital transmission of tuberculosis there is a group of cases in which heredity is unquestionable and admitted, namely those in which the fœtus shows obvious tuberculous lesions, which may be more or less general in distribution. Infection *in utero* has been observed by many medical practitioners and veterinary surgeons, including SCHMORL, GARTNER, LEHMANN, BIRCH-HIRSCHFELD, MALVOZ and JUNGE, HAHNE, BANG, BROUWIER, HUGUENIN, KOKEL, BAR and RENON, CHABRY, MONKEBERG and VERGARA, KELLER, ZITZENFREY, BUGGE, FRIEDMANN, LANDOUZY and MARTIN, CALMETTE, DE RIENZI, STOCKEL, BLOCK LELONG, HARBITZ, CHOME, WILHMANN and GREENE and others.

The lesions seen at autopsy are variable but have been classified into the three principal types¹ :—

(a) The glandular-hepatic type, which is found in more than half the cases. The lesions are situated chiefly in the abdomen and include infiltration of the liver with caseous tubercles of various sizes, miliary tuberculosis of the hepatic peritoneum, enlargement of lymphatic glands, situated at the hilum of the liver and along the duodeno-hepatic ligament, and scattered tubercles in the various organs.

(b) The disseminated miliary type, in which all the viscera are invaded with grey tubercles of varying size, and the lymphatic glands connected with the affected organs are enlarged or caseous.

(c) The hæmo-lymphatic type, in which the spleen, and the mediastinal, mesenteric and hepatic lymph-glands are enlarged; according to LANNELONGUE, in some cases there may even be changes in the bone marrow and secondary osteitis.

¹ MARCEL LELONG. "L'enfant issu de Parents tuberculeux." *Thèse de Paris*, 1925. Imprimerie de l'Aisne, a Laon.

It has also been observed that the lungs may be involved earlier and more extensively than the other organs.

The distribution of the lesions is readily explained : the bacillus reaching the blood-stream by way of the umbilical vein will be arrested at the first point at which it encounters an obstacle to its progress ; certain elements, especially the more bulky, will be held up near the point at which they enter the fœtal system, and this explains why the glandular form of the disease is the commonest. Those organisms which are carried past this first barrier will stand a fair chance of being arrested in the capillaries of the viscera, especially in the lungs, where the fine capillary network acts as a filter for particles in suspension in the blood.

Cases of tuberculosis in the fœtus are rare, almost negligible, when compared with other forms of the disease, and especially with consumption attacking subjects between 15 and 40 years of age.

I have drawn attention to this method of acquiring tuberculosis simply in order to recall the fact that KOCH's bacillus can penetrate the placenta, the impermeability of which to microscopically-visible organisms is not always complete.

B. Progressive Congenital Tuberculosis.

It sometimes happens that the child of a tuberculous mother, having been infected less extensively during fœtal life, will live after birth. Such children are generally premature, and their weight at birth is much below normal standards ; they waste, suffer from digestive troubles, the spleen hypertrophies, the lymphatic glands become enlarged and they die after a short illness from the lesions of progressive congenital tuberculosis.

If the bacilli enter the fœtal blood just before delivery occurs, or if, during labour, the placenta is torn and some of the mother's tuberculous blood reaches the fœtal circulation, no tuberculous lesion will be present in the child at birth, but he is none the less congenitally infected, and may develop progressive

tuberculosis of a more or less rapid type. But an infant may equally well be infected immediately after birth by parents who are coughing up tubercle bacilli in their sputum, so that it is impossible to say whether the case is one of hereditary transmission or postnatal infection.

C. Marasmus.

Finally, another perplexing condition may arise: no signs of tuberculosis may be present in the new-born child of a tuberculous mother, no characteristic lesion may appear, but the child gradually becomes more and more cachectic and ultimately dies. The explanation of this marasmic decline in children of tuberculous parents, without the appearance of characteristic signs of infection, has been much discussed, notably at sessions of the Academie de Medecine during the past few years.

COUVELAIRE, CALMETTE, VALTIS, L. BERNARD, ARLOING and DUFOUT, SERGENT and others have examined this problem; most of them implicate a filtrable virus, without being able, however, to prove this pathogenesis scientifically, highly probable though it appears to be.

Whatever the time at which the infant is infected, or the process by which infection takes place—whether in the course of foetal life, during delivery or after birth—whether, in short, heredity or infection after birth is the explanation, the total number of deaths from tuberculosis during early infancy represents only a small proportion of the total mortality from tuberculosis.

Out of 100 subjects dying of tuberculosis we find that among female subjects only 3·85 per cent. are under 2, and 8·3 per cent. between 2 and 10 years of age; in male subjects the proportions are 4·32 per cent. under 2, and 6·37 per cent. between 2 and 10 years of age.

The following table gives the percentage death-rate, according to age and sex, for the City of Lyons between the years 1906 and 1925 :—

PERCENTAGE DEATH-RATE FROM TUBERCULOSIS ACCORDING TO AGE AND SEX.

Age		Male	Female
From 0 to 2 years	4.32	3.85
From 2 to 10 years	6.37	8.38
From 11 to 20 years	8.00	13.81
From 21 to 30 years	14.86	21.29
From 31 to 40 years	19.77	18.36
From 41 to 50 years	20.06	12.54
From 51 to 60 years	14.33	8.02
From 61 to 70 years	7.79	7.23
From 71 to 80 years	3.77	5.16
Over 80 years	0.73	1.36
Total	100.00	100.00

Statistics should always be accepted with caution, and I do not pretend that mine are any exception to the rule. I readily admit that they may contain errors, and that the infantile mortality from tuberculosis may be under-rated. Undoubtedly some cases of marasmus, meningitis, bronchopneumonia, enteritis and peritonitis have been registered under other headings than tuberculosis, but it still seems evident that tuberculosis does not take a large toll at either extreme of life. It attacks most of its victims, if they are men, between the ages of 20 and 55, and if they are women, between the ages of 20 and 40. It is precisely at these ages that the disease is least infectious. We are driven, therefore, to the conclusion that the person destined to succumb to tuberculosis must carry in his system either the organism itself or a predisposition to the disease, though he will manifest symptoms only at the critical ages under review.

Two main theories arise out of this : heredity and infection. Either the infant is born with the organism in his body, or with an alteration in his tissue fluids which predisposes him to the disease; or else the bacillus enters the system after birth and remains dormant for some years. In the present chapter my purpose is to discuss how far the first theory can

be reconciled with clinical observations and statistics ; in the next chapter we shall see how it fits in with the results of experiment.

(3) *Clinical Observations upon Heredity in Adults.*

Evidence of tuberculous heredity has so far been obscured by irrelevant anecdotes, by the preconceived idea that infection is the sole method of transmission of tuberculosis, and by the inadequacy of observations. The following is an example of such inadequacy :—

F., aged 45, an alleged consumptive, wasted, thin, almost cachectic in appearance, had frequent attacks which prevented him from working for a week or two, after which he was able to resume work until another attack came on. His wife, aged 49, appeared to be healthy. In 1923, several years after her marriage she developed pleurisy ; in 1924 she began to cough though her general condition remained good. She did not waste, showed no rise of temperature, and her complexion remained florid ; the apexes of her lungs were fibrotic, however, the results of radioscopy were definitely positive and she had numerous tubercle bacilli in the sputum.

The doctor attending her did not consider this to be surprising. “ The husband is an old consumptive,” he said, “ and has infected his wife.” What was not stated in the history was the fact that the wife had 13 brothers and sisters, 10 of whom had died, the majority from tuberculosis. It could not have been the husband who infected the brothers and sisters, since most of them had died before he married.

I do not, of course, attempt to adduce the foregoing facts in support of the theory of heredity. Far more significant, from the point of view of heredity, are observations of the kind quoted below, which many practitioners will be able to duplicate from their own experience.

Mrs. V., aged 24, in perfect health, was six months pregnant when her husband died of consumption ; the family being well-to-do, every care was taken to

avoid infection of the child, who was brought up in the country under favourable sanitary conditions, and with strict precautions against infection. Everything was done to keep this child out of range of tubercle bacilli, but he died from tuberculous meningitis when he was four years old. This occurred fourteen years ago, and the health of the mother has remained excellent; she never showed the slightest symptom suggestive of tuberculosis, even in a latent form, and radiosopic examinations of her thorax have always given negative results.

Let me quote here another example, which should properly have found a place in the chapter on infection, but which may be included here as a curiosity, and because it is the exact complement of the example quoted above.

Mrs. A., aged 32, had been pregnant for two months when her husband, who was in good health, was killed in a factory accident; towards the end of pregnancy she made the acquaintance of a man who was suffering from bilateral, ulcero-caseous pulmonary tuberculosis of a slowly progressive type, and who had tubercle bacilli in his sputum. The pair lived together as husband and wife, until it became legally possible for them to marry, which they did. The child was born into a tuberculous environment, under deplorable sanitary conditions, and no precautions were taken to prevent infection; the husband expectorated freely, and having grown fond of the baby used to kiss it repeatedly, and had the task of looking after it while the mother went out to work, the husband being unfit to do so. He died when the child was eighteen months old; fifteen years later mother and child were in perfect health.

ZOPPELIUS, LANDOUZY, BASSY, SANSON and others have observed that children of consumptives, though separated from their parents immediately after birth, are nevertheless prone to tuberculosis; and HUTINEL records the same finding among foster children born of tuberculous stock, who, when placed in country

homes by the *Assistance Publique*, may withstand the disease for some time, but are ultimately decimated by it.

MANGIAGALLI writes on this subject : " Observation shows that even if the children of consumptive parents are removed from infection, and even if they are sound at birth, tuberculosis attacks them more readily than others."

The influence of paternal heredity where the mother is clinically sound has been noted by many authorities, including CERF, DAMASCHINO, BASSY, BANG, FIEUX, HUTINEL, LANDOUZY, SANSON, OUTREPONT, RILLET and BARTHEZ, ZOPPELIUS and others. In certain examples quoted by these writers, an attempt was made to safeguard the children against infection by preventing them from having any contact with their fathers.

No proof of heredity could be more to the point than that furnished by HUTINEL when he said : " Some children, born of a sound mother and begotten by a consumptive lover, become tuberculous, while older children in the same family begotten by the legitimate and healthy father, remain free from the disease."

PLA Y ARMENGOL quotes three careful observations made upon married couples in which the tuberculous father died before the birth of his child ; the children developed tuberculosis despite the fact that their mothers were healthy and that they were given every care.

Let me once more draw attention to an argument in support of the theory of heredity, namely, the similarity in the distribution of lesions, and the identical age-incidence of the disease found in members of the same family. Evidence of these two phenomena has been collected by BREHMER, BALDWIN, KURTNY, FISCHBERG, FRIEDMANN, PIERY, MOLLER, AUBURTIN, TURBAN, PHILIBERT and others. It must be recognised that these phenomena are not found in every family affected with tuberculosis ; innumerable exceptions can be quoted ; but they appear to

occur too frequently to be the outcome of mere coincidence.

Numerous examples could be quoted, if one took the trouble to collect them, of persons suffering from quiescent tuberculosis, who never coughed up tubercle bacilli in the sputum, but whose offspring, despite the most elaborate precautions, developed tuberculosis.

This was the case with Mrs. H., who had suffered from caseous tuberculous glands during infancy and had developed at 15 a left-sided coxalgia which progressed to complete recovery, so that she reached adult life in perfect health ; on radiography, her lungs showed no sign of a lesion, and there were no indications of tuberculosis other than the healed scar in the right submaxillary region and a slight limp. At the age of 22 she married a healthy man of 30, and gave birth to three children ; both parents remained in perfect health, but in view of the mother's previous history the children were carefully supervised and protected from contact with any tuberculous persons. In spite of this, one child died of meningitis at the age of 5, and a second from consumption at the age of 12.

Another example is to be found in the history of the M. family, consisting of father, mother and 6 children. The parents appeared to be healthy. Five or six years before her marriage, however, the mother had had an attack of bronchitis which lasted for three months and then disappeared, leaving no signs in the chest ; she never coughed, and showed no pulmonary, digestive or renal symptoms which could suggest a source of tubercle bacilli. Five of the six children died in succession, but at fairly long intervals, from rapidly progressive forms of consumption, despite the fact that measures were taken to prevent contact between each ailing child, in turn, and his remaining brothers and sisters, as soon as signs of tuberculosis appeared.

Another case is that of Mrs. G. and her husband,

in whom no evidence of tuberculosis could be detected. Three children were born to these parents, who paid particular attention to matters of hygiene ; the father was a well-informed man whose work brought him into contact with the medical profession, and he was careful to protect his family against the chance of infection. The family lived in a suburban villa and were therefore situated under ideal conditions as far as avoidance of infection was concerned. Ten years after the birth of the last child the mother developed a curious contraction of her right foot. Various medical authorities were consulted, but none of them diagnosed tuberculosis ; the contraction, though crippling to the patient, was thought to be purely functional, since the woman had been of the neurasthenic type for many years. Two of the children in this family, aged 22 and 24 respectively, died from tuberculous meningitis, death occurring within a few days from the onset of the disease in each case ; and several years later the mother died of generalised tuberculosis.

Neither the mother nor the children could have provided a source of tubercle bacilli which might have been responsible for infection from one to the other. It is more likely that the children were hereditarily affected, and that in the mother, who had long been tuberculous though not infectious, the latent disease finally manifested itself in the undiagnosed contraction of the foot. It was only later, long after the death of her children, that a generalised spread took place.

Authorities on tuberculosis who deny the influence of heredity ought to be able to offer some explanation of cases of this kind, which do not appear to be at all rare. They should also explain why the thousands of persons composing the medical and nursing staffs of sanatoriums and hospitals for consumptives, who live continually in a tuberculous environment, never contract the disease ; whereas persons removed from all chance of encountering the disease, like those in the examples quoted above, and hedged about

with every precaution, nevertheless become tuberculous. Heredity can explain these phenomena, but they remain inexplicable by the theory of infection.

(3) *Considerations drawn from Statistics.*

If we wish to know the limits within which tuberculosis is hereditary we must first decide what proportion of patients suffering from the disease came of tuberculous parents or parents who, before the birth of their children, showed symptoms which could be ascribed to tuberculosis.

A direct answer to this question would obviously provide an argument of great importance in the discussion on the inheritance of tuberculosis; but, incredible though it may seem, not a single observer has furnished information on this point.

A good many inquiries have certainly been undertaken in this branch of tuberculosis demography, but they have been conducted so unsystematically and unscientifically that the results are valueless. The discrepancies in the estimates quoted in the following table give a clear idea of the unreliability of work in this field:—

THE INCIDENCE OF HEREDITY AND HEREDITARY-PREDISPOSITION,
AS ESTIMATED BY VARIOUS AUTHORITIES.

Name of observer	Percentage of cases in which a hereditary factor may be implicated
GIALUSSI	10
LOUIS	11
BILLET and BARTHEZ ..	15
LIBERT	16
PIORRY	25
ANCELL	
PIDOUX	
WALSHE	
HERARD and CORNIL ..	38
BREQUET	40
MILL	50
COTTON	
BOKENDAHLE ..	70
HOMAN	
PORTAL	75
RUFZ	82
GRUNBERG	95

Why should the estimates given vary so widely? The figure obtained depends upon the care and conscientiousness with which the observer carried out his investigations. Those who have taken the trouble to scrutinise the facts of the family history of the patient with particular care, who are not content with the vague and inaccurate information supplied by patients themselves or by their relatives and friends, have found that in most cases the disease can be traced back to the parents.

Among those who have inquired most conscientiously into the influence of heredity in tuberculosis from the ætiological, statistical and clinical points of view, must be included GRUNBERG, who investigated 568 families; in 472 of these the parents, grandparents or children were tuberculous, and in 96 the parents were unaffected; the latter group was included as a control. GRUNBERG concludes that the absence of a tuberculous heredity is extremely rare in tuberculous people; he found only 4·8 per cent. of consumptives with parents who were free from the disease (and he did not confirm this by radiography); *whereas he found evidence of parental disease in 95 per cent. of cases.*

My own experience has been that, whenever thorough medical and radiological examination of the parents could be performed, evidence of parental tuberculosis was invariably forthcoming. Unfortunately in many cases such an examination cannot be performed, the parents being dead or not being available for other reasons, or else the opportunity is lacking for thorough investigation.

From the time of HIPPOCRATES until the present day, clinicians have noted that most consumptives come of tuberculous stock, and this fact has been observed with a frequency varying with the care with which the inquiry into the family history has been conducted. Even those who do not perform this task systematically, but are content with the vague and frequently erroneous statements of patients

and their friends, find a high proportion of cases in which heredity can be implicated. Where an observer has the will and the opportunity to get to the bottom of things, this proportion will be found to reach nearly 100 per cent.

I am aware that some observers will contend that this is due not to the fact that the patients have inherited the disease, but to the fact that they have been infected after birth; this argument will not hold water, however, for reasons which I have already set out, and in view of the many cases in which, despite elaborate precautions to avoid infection, children of tuberculous parents develop tuberculosis in their turn, even when born after the death of a consumptive father. There are, in addition, patients suffering from closed lesions (such as Pott's disease, osteitis, synovitis, arthritis and tuberculosis of lymphatic glands prior to fistula formation) who cannot disseminate bacilli; such patients are nevertheless a source of danger, inasmuch as their children, in spite of vigorous precautions to prevent infection, will eventually develop the disease which was latent in them at birth.

I am anxious to learn of examples in which no evidence of tuberculosis could be detected in the parents of the patient in spite of thorough scientific examination. So far, not a single case of the kind has been forthcoming, and I have been seeking one in vain for the last few years. No doubt a case of this kind will come to light some time, since infection can never be an impossibility, and must actually occur on certain rare occasions. But to establish the fact of infection as a common occurrence thousands of such cases, properly confirmed, would have to be produced, so many and so prolific are the sources of tubercle bacilli scattered throughout the world.

What arguments can be urged against this fact : *When evidence of heredity is sought in cases of tuberculosis, it is found in the vast majority?*

A few observers claim that they found a tuber-

culous heredity in only a small proportion of cases examined, and quote this fact in support of the theory that infection had occurred in those cases where the family history was negative. Prof. CALMETTE, especially, points out that in certain children's hospitals no evidence of parental tuberculosis was obtained in 52 per cent. of cases. It is worth noting that the presence of tuberculosis was easily recognisable in the parents of 48 per cent. of them. Of the remaining 52 per cent. a certain number were probably infected in early infancy; I have already admitted the occurrence of this mode of infection. But against these figures I must offer the usual objection: the parents of these children have not been carefully examined and radiographed in every case; it is probable, if not certain, that they were not subjected to any of the tests necessary to exclude the possibility of hereditary transmission of the disease.

I cannot, therefore, accept these figures. Tuberculosis is extremely common in the parents of tuberculous patients, and the cases must be numerous in which the disease passes unnoticed in the parents.

During 1929, DUMAREST drew the attention of clinicians to the latent form of the disease, and since I began to seek such cases among the parents of tuberculous patients I have been astonished at the frequency with which they occur.

Out of the last 178 tuberculous cases which have attended the clinical wards of our laboratories, under the care of Dr. GELIBERT, 17 were seeking advice for ailments other than pulmonary conditions; in these 17 cases, tuberculosis was discovered by chance on examination. The following is a typical example:—

A woman, aged 22, came up a few days before her marriage complaining of slight gastro-intestinal symptoms. She had no fever, cough or sputum, no pains in the chest, no night sweats, and her general condition had shown no signs of deterioration; her astonishment was extreme when she was told that she

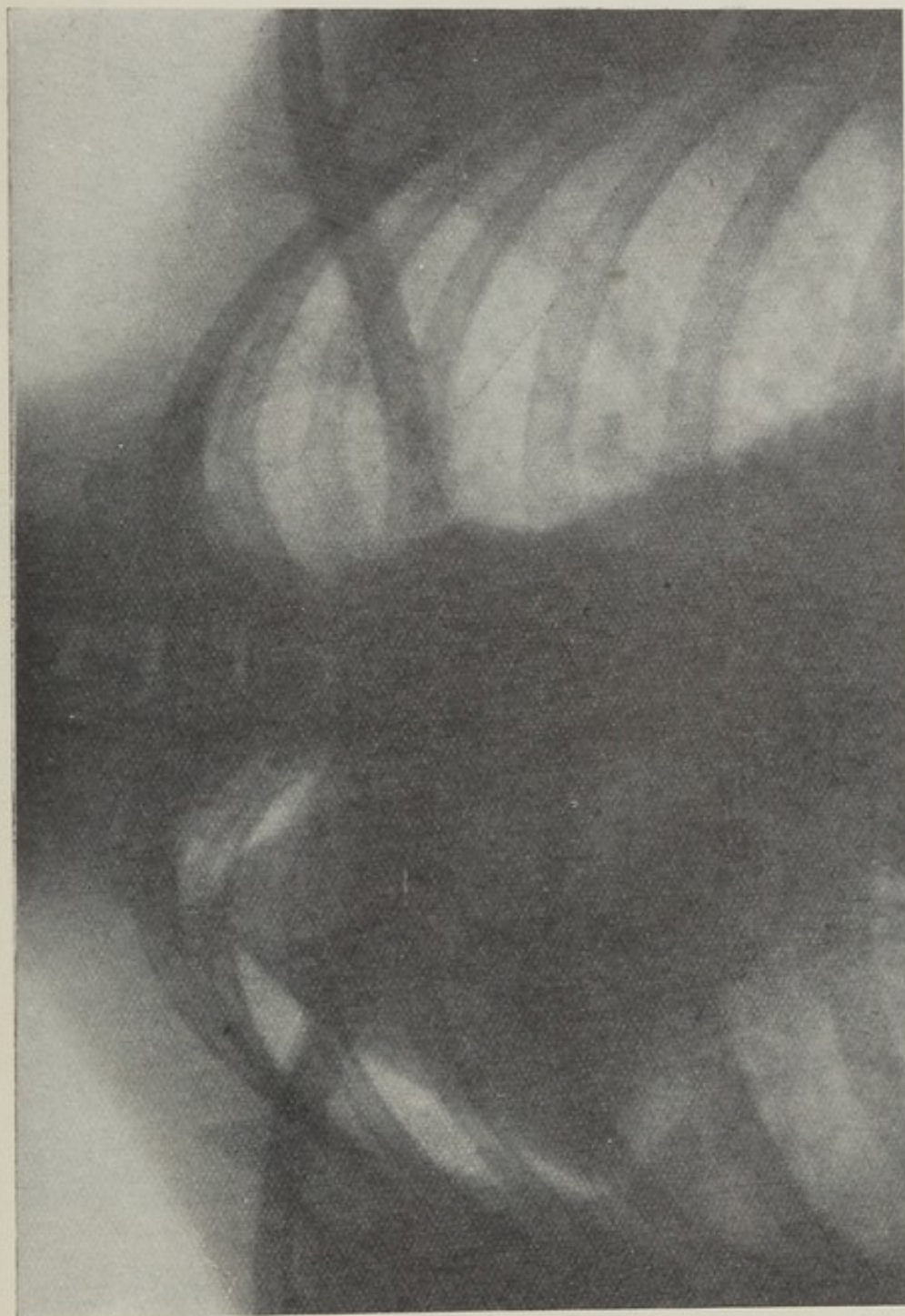


FIG. 20.—Extensive pulmonary tuberculosis in a woman aged 22. The patient showed no symptoms of tuberculosis, and the disease was only detected on examination. Radiography following the initiation of artificial pneumothorax.

was suffering from a serious pulmonary lesion and would have to postpone her marriage. In point of fact examination revealed extensive fibrosis, and on

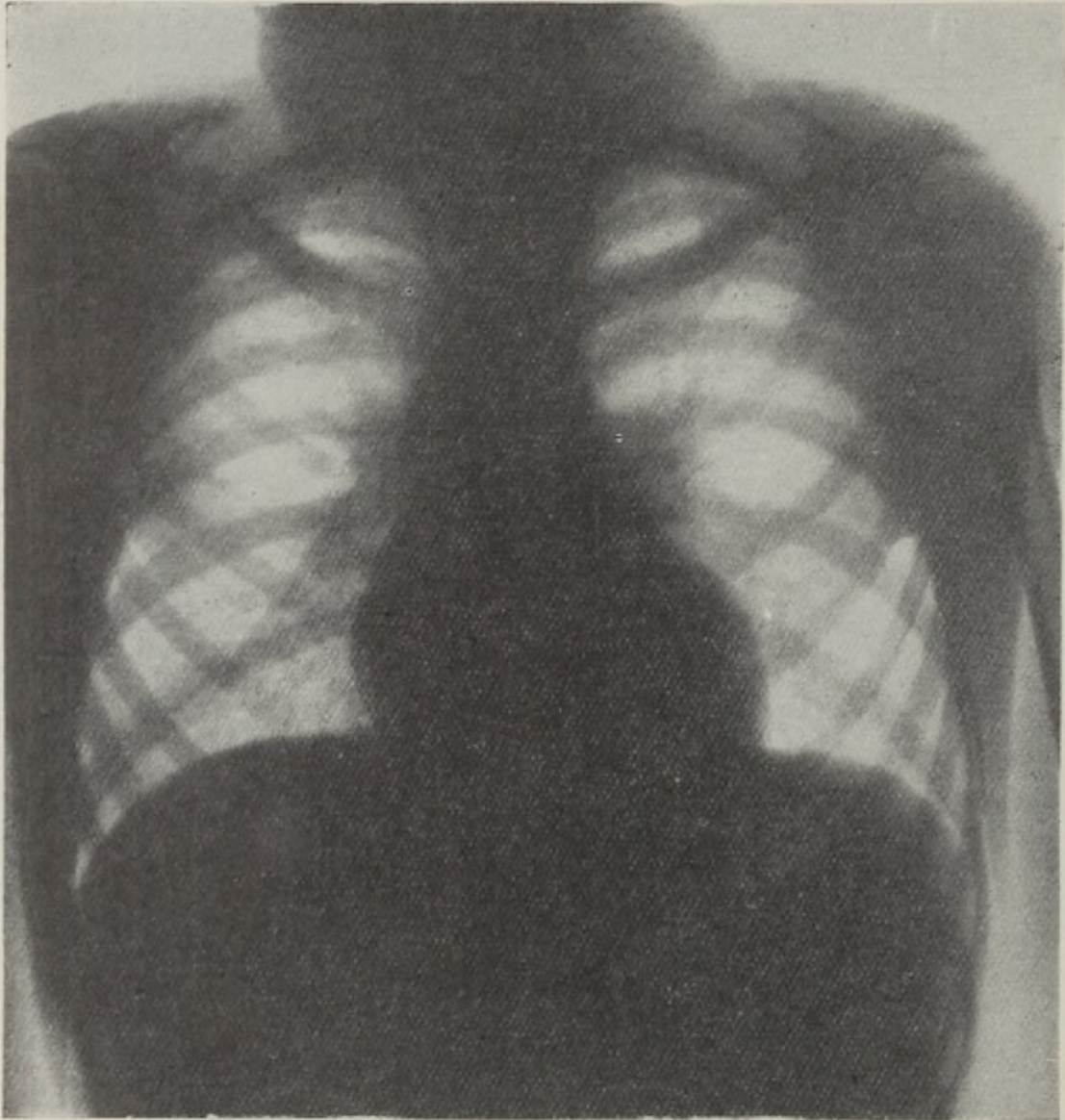


FIG. 21.—Enlarged glands at the hilum on both sides, in an infant who had developed occasional rises of temperature without other symptoms. A few crepitations heard at the left apex.

auscultation fine crepitations were heard in the right subclavian region. The radiosopic signs were so definite that I have had the film reproduced in fig. 20, which indicates the amount of fibrosis which may develop without the subject being aware of the condition.

Figs. 22, 23, 24, 25, 26 and 27 illustrate other tuberculous lesions which were unsuspected by the

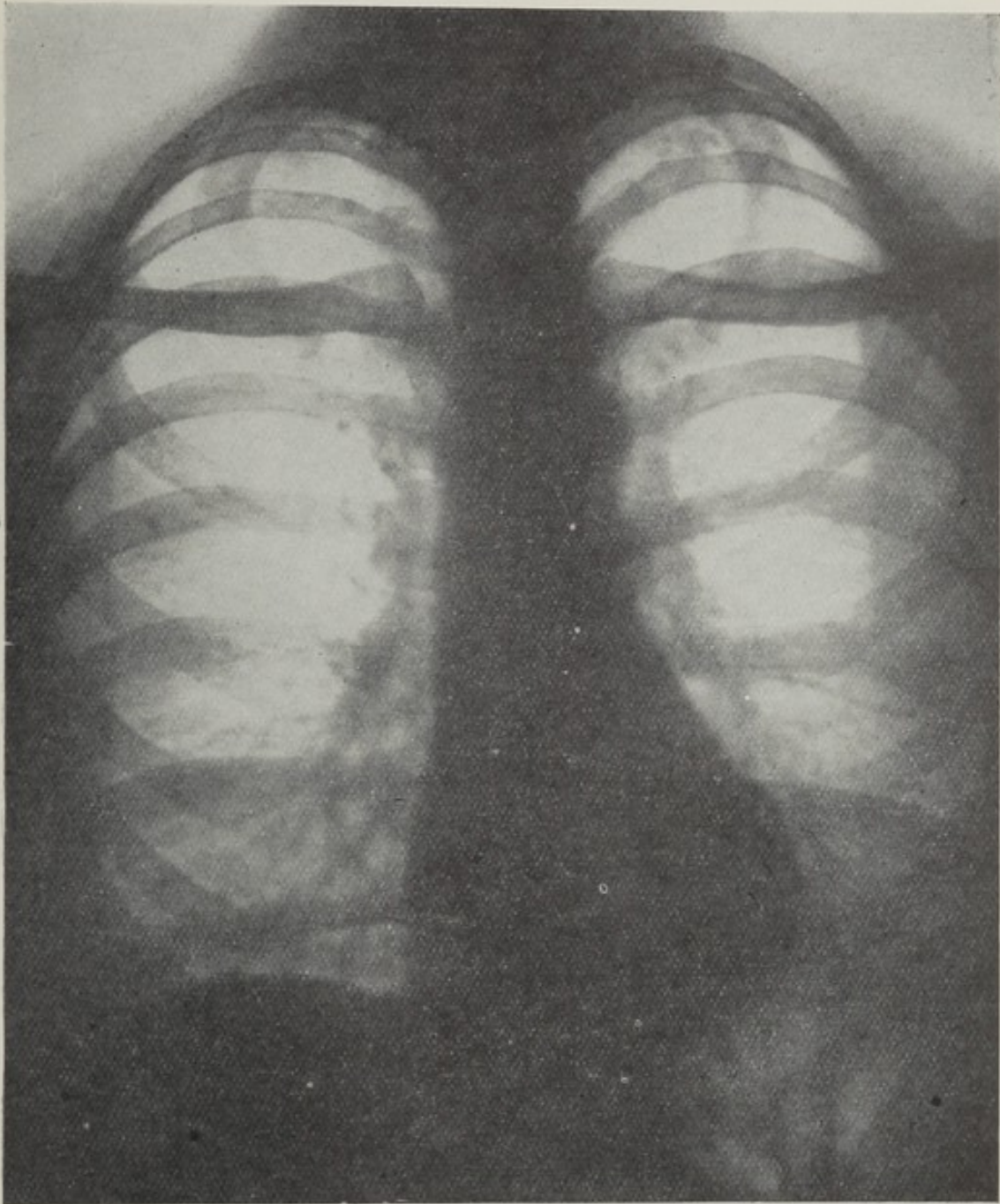


FIG. 22.—Enlarged glands at the hilum and peribronchial lesions, with definite signs on auscultation. The patient had no cough, fever or expectoration. She came to the clinic complaining of palpitations.

patients themselves, and which support the view that the disease must often pass unnoticed. These types of tuberculosis, unsuspected by the affected person

and detected only upon examination seem, like those described by Dr. DUMAREST, to be slowly progressive fibrous lesions from the outset; in other cases the

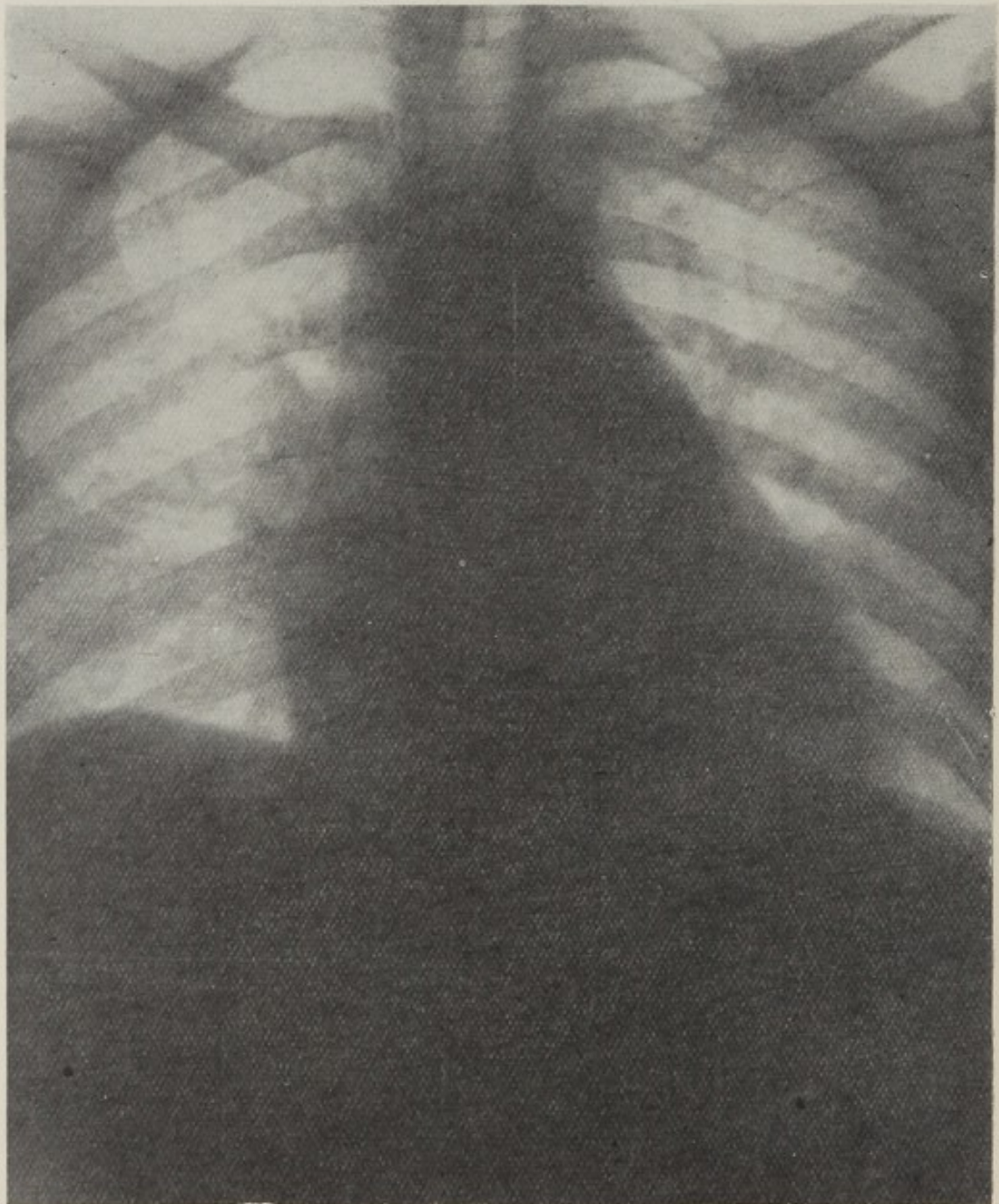


FIG. 23.—Lesions found on examination of an infant brought to the clinic for anæmia.

lesions are situated in the glands at the hilum of the lung, or deep in the pulmonary tissue, not extending to the pleura, and not communicating with any

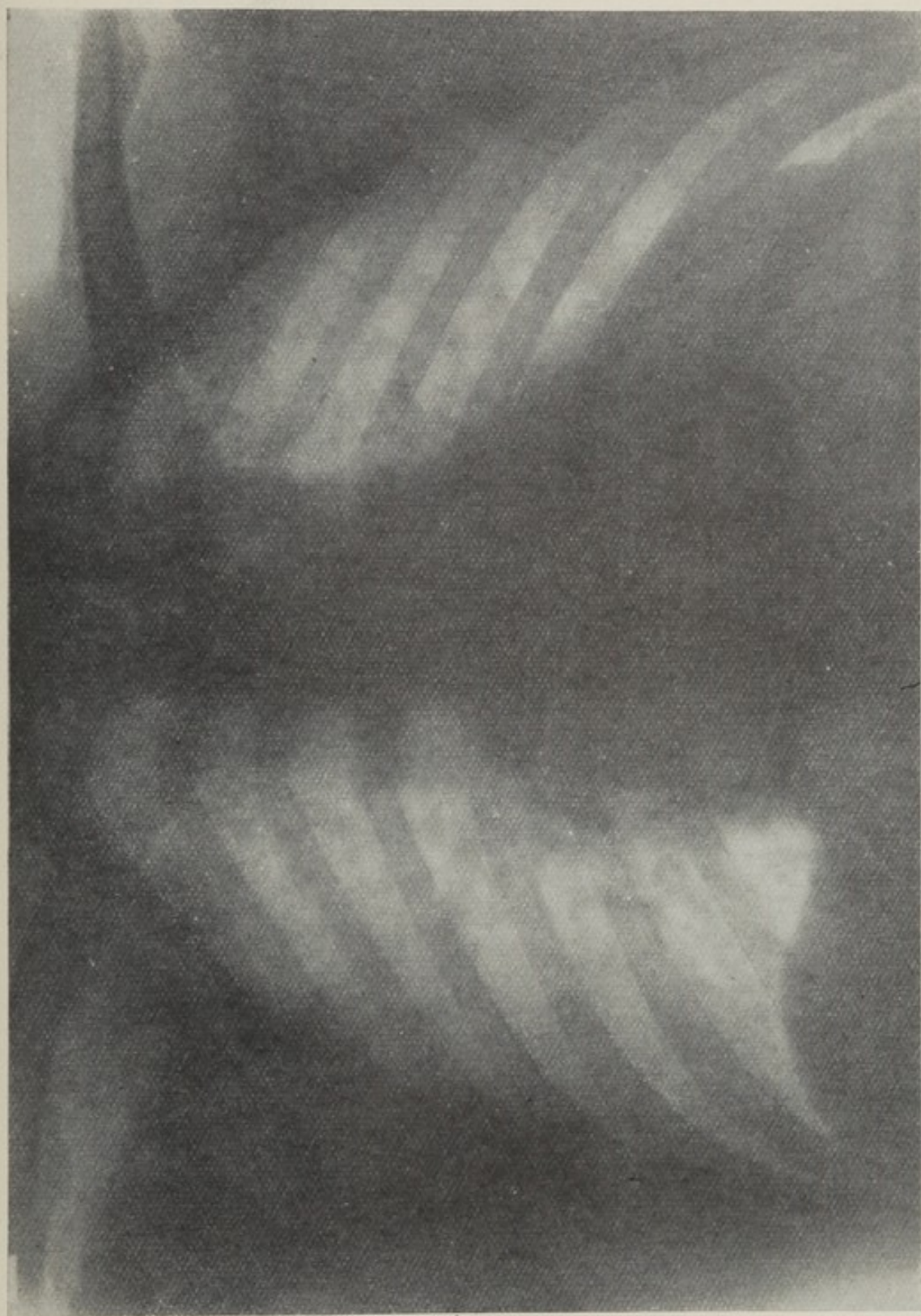


FIG. 24.—Bilateral lesions found on examination of a patient who had no cough, no expectoration, and no other symptoms of any sort.

bronchi, apart from the minute terminal bronchioles.
Some of these patients may recover spontaneously,

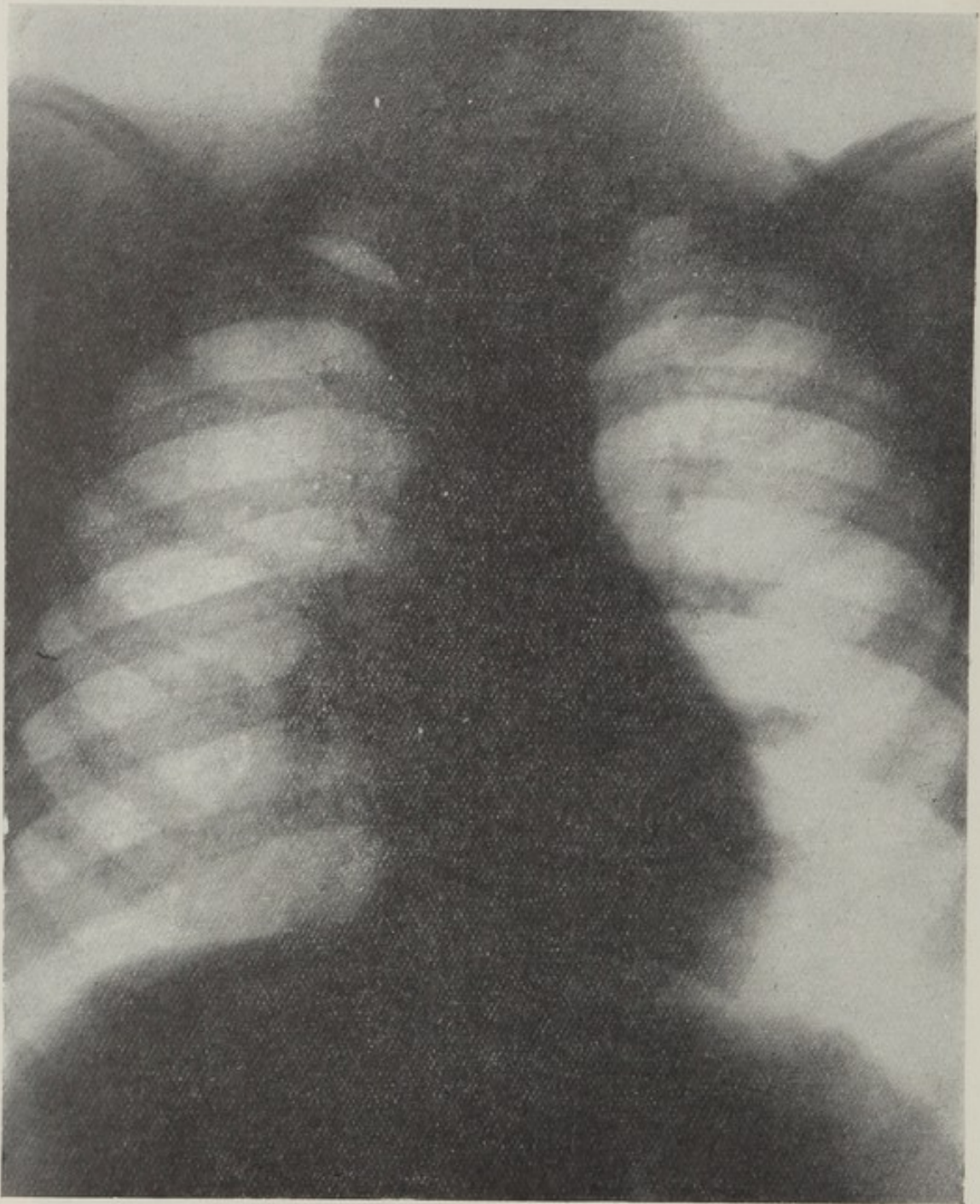


FIG. 25.—Unsuspected hilar lesion; the patient complained of no symptoms, and the condition was discovered radiographically.

in which case if their children develop tuberculosis the hereditary factor will be passed over unless the parents have been examined radiographically.

Other cases may be quoted which show how difficult it is at times to trace a history of tuberculosis in the parents of a patient.

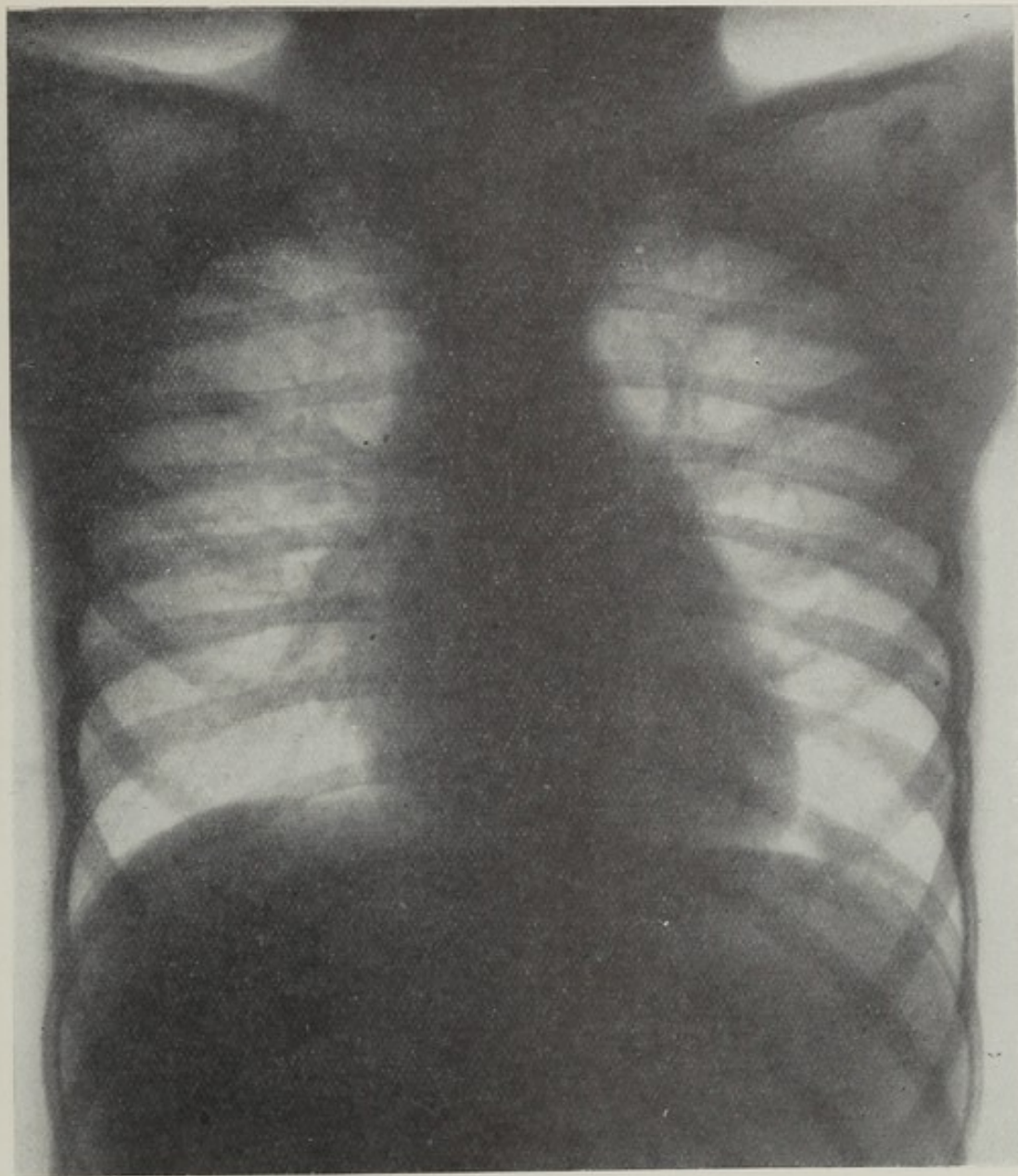


FIG. 26.—Lesions of the hilum and of the left base detected on auscultation no other signs.

Mr. C., for example, aged 17, was suffering from a fibro-caseous lesion of the right apex, and had numerous tubercle bacilli in his sputum. He was first examined by a friend and colleague of mine who,

after the usual interrogation of the patient and his mother, made a note to the effect that both parents were in excellent health. He concluded that there

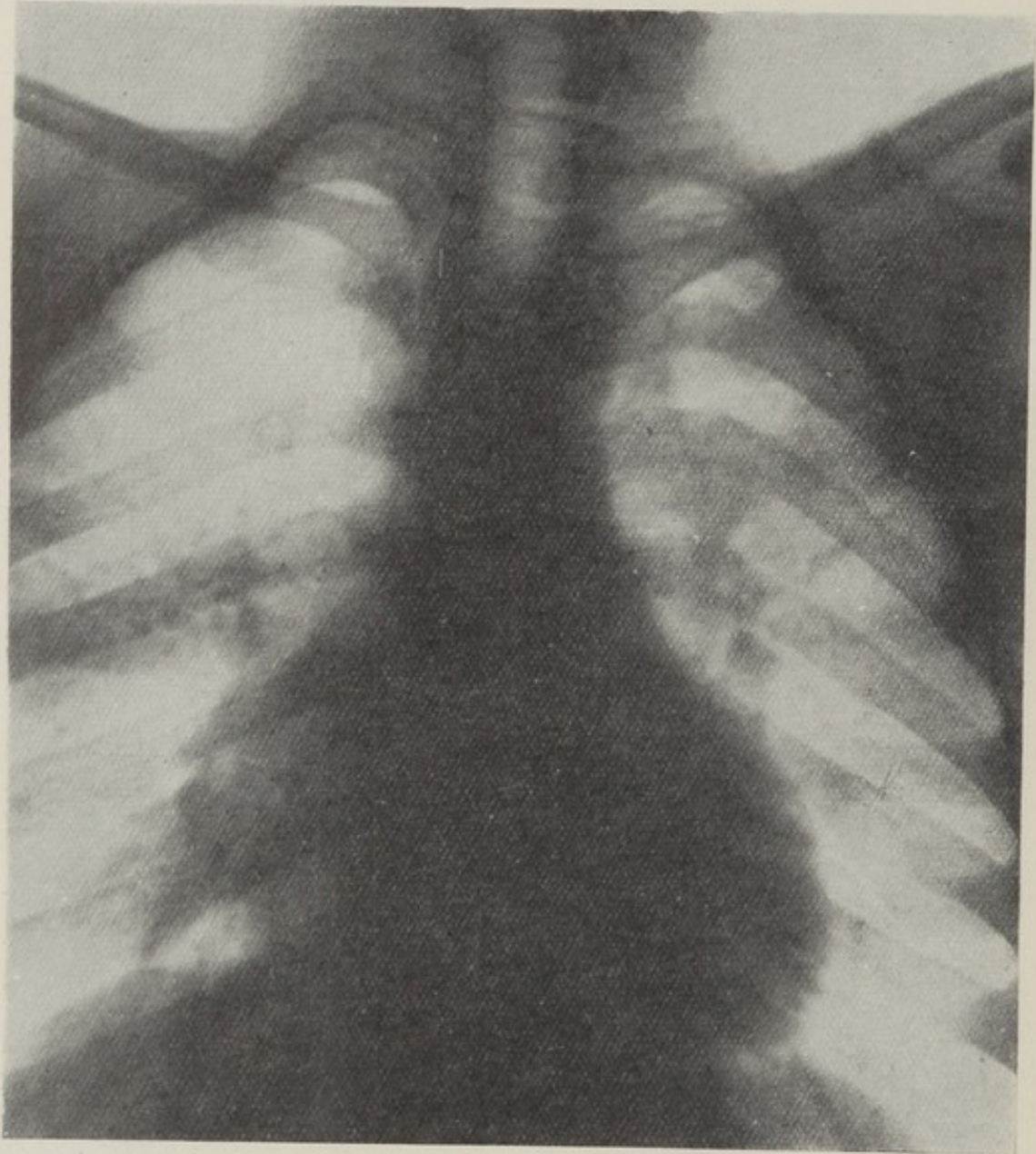


FIG. 27.—Bilateral lesions in a case showing no symptoms other than wasting.

was no family history of tuberculosis. But a consumptive nephew had lived with the family for several months and had finally died in their home, and my colleague came to the conclusion that this was a case

of infection between cousins—an interpretation which nearly every medical practitioner would have put on the facts, since most of them are satisfied with a cursory investigation of the family history.

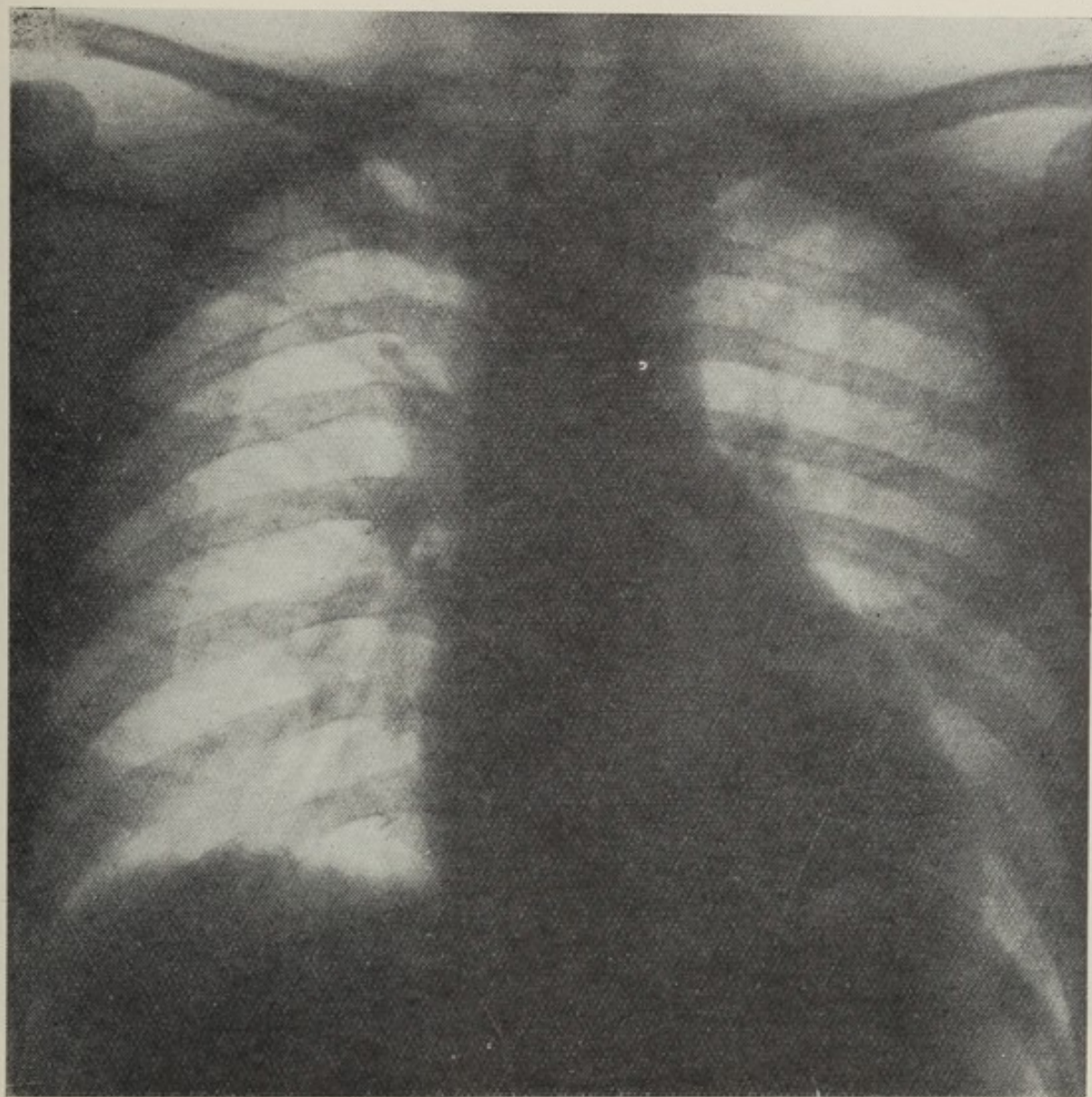


FIG. 28.—Mr. C. Unsuspected tuberculosis.

Not having had an opportunity to examine the father of this patient, I succeeded in persuading the mother to be radiographed, and found that she had definite signs of old pulmonary lesions. I questioned her afresh, and at last elicited the fact that during

the war she had chronic bronchitis which lasted three years and for which she was treated by a professor of the Lyons faculty.

A second case is that of Mr. S., aged 47, who brought his 17-year-old son up to the clinic for examination. The father formally declared that his

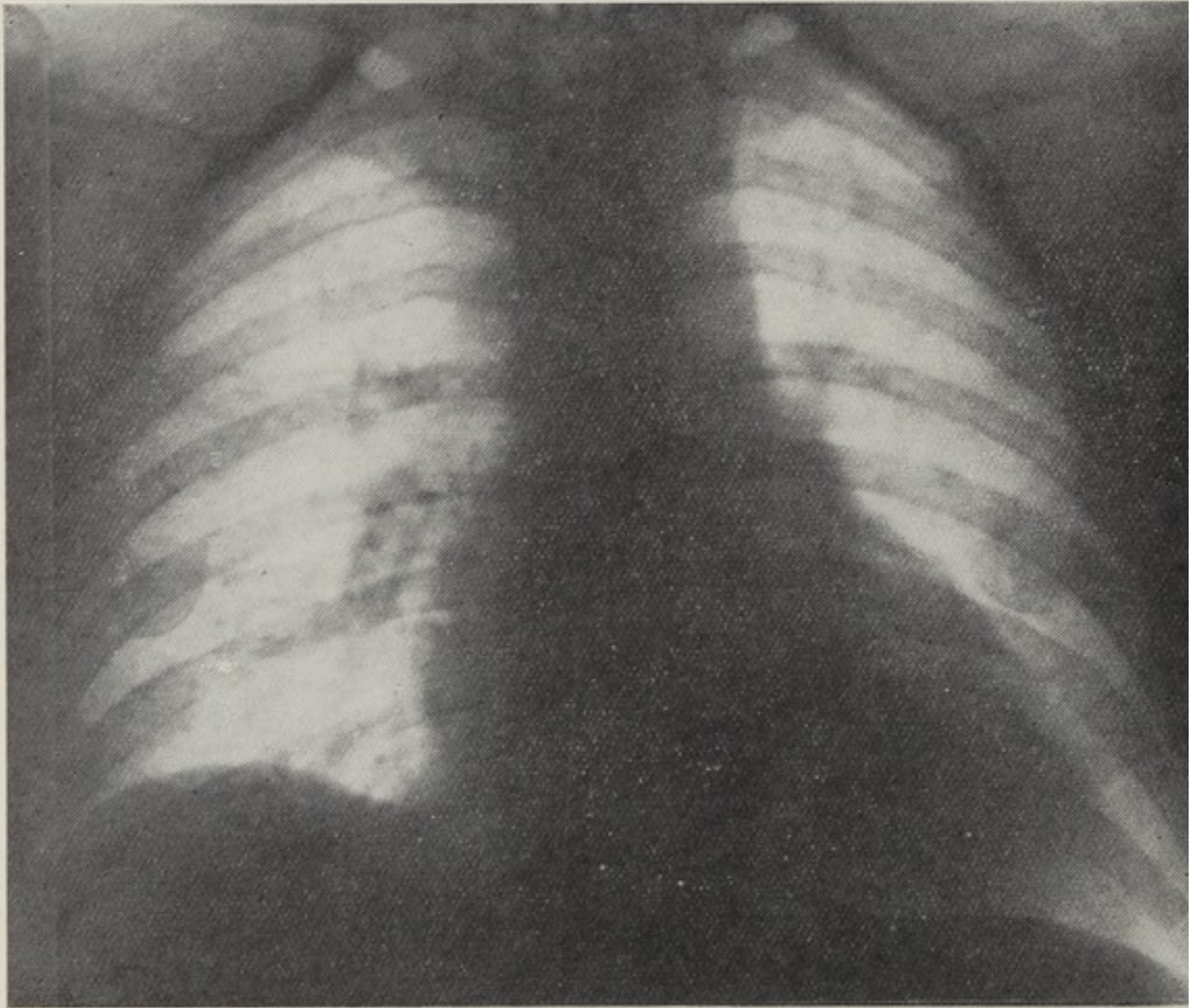


FIG. 29.—Mr. S., senior.

wife was in perfect health and that he himself had never had a day's illness in his life, that he had no cough, and had never had any signs of tuberculosis. His flourishing appearance seemed to corroborate his statements. I asked him to allow us to X-ray him at the same time as his son, who had had a left-sided

pleurisy some months previously, and in whom, as a result of physical examination, I suspected a lesion at the left apex.

I submitted the two radiographs (figs. 29 and 30) to my colleague; he did not know the patient or his father and I gave him no particulars about them. I

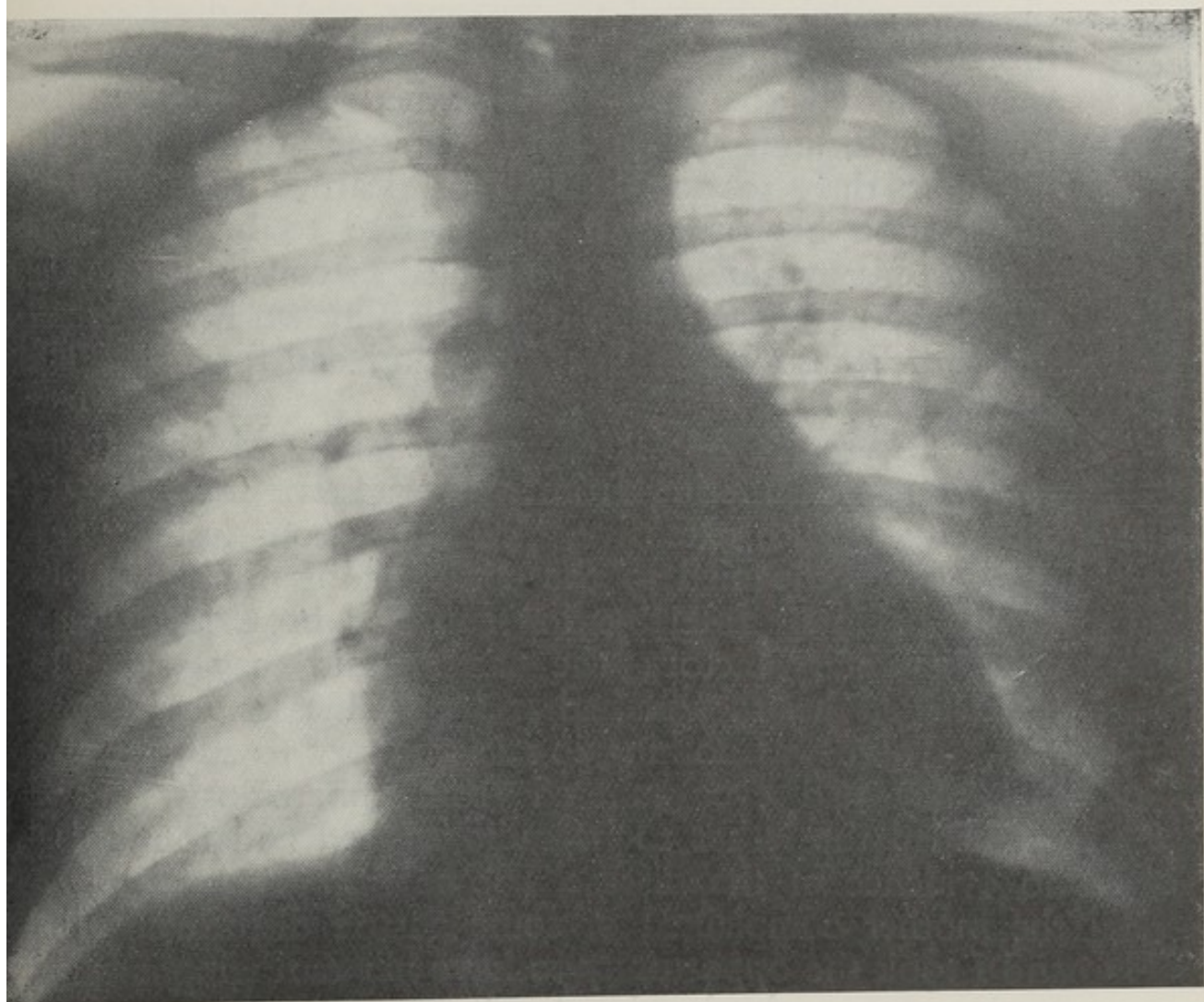


FIG. 30.—Mr. S. junior.

asked him to say which of the radiographs belonged to the patient, and without hesitation he pointed to that of the father. It will be noticed that there is a striking similarity between the two radiographs, but the lesions appear to be more marked in the apparently healthy father than in the ailing son.

Another case, which illustrates a singular type of mistake, is that of a young man, Mr. C., aged 24, suffering from rapidly progressive bilateral lesions with cavitation. He was positive that the health of his parents was excellent. I tried repeatedly to obtain an opportunity of examining his parents, but failed. While he was undergoing a course of chrysotherapy, which checked the progress of the disease, his brother, who had also developed tuberculosis, was admitted to hospital, and died there within three months. It was not until I had seen the patient on more than 30 occasions that I learned that the information he had given me referred to his step-mother, his own mother having died of consumption at the age of 34. Her son had never known her, for she had died soon after his birth, and had forgotten all about her.

No less remarkable is the case of Mr. M., aged 17, who was suffering from a progressive form of tuberculosis with extensive, bilateral caseous lesions. He was accompanied to the clinic on his first visit by his parents. Interrogation supplied no evidence of a hereditary factor; the parents said they were in excellent health and had had no illnesses in the past. There was nothing in their history to suggest that they had ever suffered from tuberculosis. I persuaded the father to be radiographed and found no evidence of the disease. Some time afterwards the mother complained of some gastric disturbance and I took the opportunity to have her radiographed in her turn. Again the result was negative—no evidence of tuberculosis!

The case interested me particularly, since I had had the opportunity to investigate the parents of my patient and had failed to find any evidence of a hereditary factor. My astonishment, therefore, was considerable when, having got the son out of the way during one of the last visits, in order to warn the mother of his serious condition, she informed me that she was not his mother at all, but that the boy

was unaware of this and was not to be told. His real mother had died of acute tuberculosis at the age of 29.

The caution with which the statements of patients should be accepted is strikingly emphasised by such an experience. Cases of the kind are by no means exceptional.

In my own experience, which has been especially directed towards the investigation of heredity, positive signs of tuberculosis in the parents have been found constantly, and I am fully in agreement with the findings of GRUNBERG, who obtained evidence of tuberculous heredity in 95 per cent. of the cases he investigated, without having recourse to X-ray examination. I believe that anyone who pursues the same line of inquiry will arrive at similar conclusions.

In the meantime I cannot accept statistics which have been compiled without due consideration, and which do not cover a complete examination of the parents of the patients, including the evidence afforded by radiography. Statistics of the kind cannot be regarded as providing an argument against the theory of heredity. As far as I am concerned, the facts must be allowed to speak for themselves.

I should like to recall the work of a biologist, who, during his short career, investigated the question of heredity. I refer to the unfortunate CH., who, after various experiments on the larger animals, was firmly convinced that tuberculosis was not hereditary; out of 25,000 calves which he examined he found only four which were tuberculous at birth.

He had reason to recant, poor fellow.

"I am done for," he said one day to JANETEAU, a veterinary surgeon of Blagnac; "my family all die of tuberculosis. My father and mother died of it, and my sister and I will soon be carried off in the same way."

In spite of his forebodings, he married and had two children. The precautions with which they

were surrounded may be imagined, but his prediction came true : his widow is the only survivor ; tuberculosis was responsible for his death and for the deaths of his sister and his two children.

Examples of this kind could be multiplied indefinitely. In Appendix II at the end of this book (p. 240), the reader will find statistics relating to the last 169 married couples suffering from tuberculosis whom I have had the opportunity of investigating. He will notice that out of this series of 169, no less than 148 couples became the parents of tuberculous children, the number of children affected being 187. There are only 21 couples who have no tuberculous children at the present time, but it should be noted that among these there are several young couples who will undoubtedly become the parents of tuberculous children in the future, and there are a certain number of sterile marriages.

The incidence of tuberculosis in the children of tuberculous parents, indicated by these statistics, high though it is, lags behind the true figure, both for the reason just set forth, and because in all these families there are a certain number of children who have not yet reached the age at which the manifestations of tuberculosis are commonly seen for the first time.

Are not the facts overwhelmingly in favour of the Hippocratic dictum : *A consumptive is born of a consumptive* ?

The conclusions with regard to tuberculous heredity to be drawn from clinical facts and statistics may be summarised as follows :—

(1) Apart from rare but definite cases of infection *in utero*, where the fœtus is born with obvious clinical lesions, patients are encountered in the course of clinical experience who develop tuberculosis during infancy or adolescence, in spite of the fact that every precaution is taken to protect them from infection ; these cases can only be accounted for on the theory of the congenital transmission of the bacillus, or of an inherited predisposition to the disease.

(2) Interest attaches to figures showing the percentage of tuberculous patients who come of tuberculous parents ; this percentage appears to be considerable.

(3) The literature published on the subject so far is strikingly inadequate ; the question calls for reconsideration, with such scientific safeguards as will enable statistics to be presented and assessed at their true value.

(4) The fact that the parents of a tuberculous patient are infected with KOCH's bacillus does not necessarily imply that the disease was inherited ; infection might have occurred during the post-natal period.

(5) In order to discriminate between congenital transmission and infection after birth an investigation would have to be made to find out what becomes of the children of tuberculous parents between 25 and 30 years of age, assuming that they are segregated from their parents at birth and placed in an environment free from tuberculosis.

(6) When evidence of tuberculosis is sought in the parents of tuberculous patients it is found in almost every case.

As far as my own experience goes, whenever I have had the opportunity of examining the parents of a patient clinically, radioscopically and radiographically, I have invariably found evidence of tuberculosis.

An objection is sometimes made on this point. "It is not surprising," I am told, "that you find evidence of tuberculosis in the parents of your tuberculous patients, since after a certain age everyone shows more or less evidence of the disease."

An attempt to prove this assertion is based on the two following arguments : the frequency with which the tuberculin reaction is found to be positive in adults, and the common discovery of tuberculous lesions in the course of post-mortem examination of old people, in hospitals.

Although the tuberculin reaction is frequently encountered it is far from being constantly present, and in any case it is not a sign of tuberculosis at all. As I have shown, when dealing with allergy, it is found in persons who have never shown the least signs of tuberculosis, however trifling. To reckon as tuberculous all the people who had positive skin reactions would be like saying that all those whose serum agglutinates Eberth's bacillus are suffering from typhoid fever.

As to the presence of tuberculous lesions in old people, let me point out that the inmates of a hospital correspond to the social class whose lack of physical stamina renders them particularly liable to the disease ; moreover, the lesions so often attributed to tuberculosis are seldom submitted to sufficient investigation to enable anyone to declare with certainty that they are tuberculous rather than simple inflammatory lesions.

Lastly, in the process of thorough clinical and radiological examination of patients who come seeking advice for the most diverse conditions, it is impossible, in a large number of cases, to find the least evidence of tuberculosis. To say that everybody is tuberculous is another of those inaccurate statements with which the conventional theory of infection is laden.

CHAPTER VII.

HEREDITY (*continued*).

Discussion of Experimental Findings connected with Inheritance of the Tubercle Bacillus.

THE revival of the idea of infection, which at present is the accepted view of the ætiology of tuberculosis, is the outcome of VILLEMEN's famous experiments proving that the disease was inoculable. Owing to extensive and erroneous interpretations put upon the facts observed by VILLEMEN, inoculation has been confused with infection. The fact that tuberculosis can be transmitted by inoculation gives no ground for the belief that it is transmitted by simple infection.

It is well known that the return to the theory of infection was hastened, first by KOCH's discovery, and then by the results, for the most part negative, of the search for tubercle bacilli, immediately after birth, in the offspring of tuberculous stock; it was further accelerated by the failure of attempts to procure congenital transmission of the disease in animals.

I shall not attempt to describe in detail the innumerable investigations which have been made into the question of heredity; in some, the tubercle bacillus has been sought in the spermatozoon, the ovum, the placenta or the blood, while in others attempts have been made to discover it in the fœtus or the newly born animal.

ALBRECHT, CAVAGNIS, and later LANDOUZY and MARTIN, DOBROKLOWSKI, SIRENA and PERNICE, FOA, AUBEAU, KURT-JANI and HAUSER infected animals by injecting them with the seminal fluid of consump-

tives and the seminal vesicles of tuberculous guinea-pigs ; or they demonstrated the presence of tubercle bacilli in the seminal fluid, testis or prostate of tuberculous subjects ; or else they were able to demonstrate infection of the seminal fluid following the injection of a culture of tubercle bacilli into the testicle of the guinea-pig.

GARTNER and MAFUCCI, FIORE SPANO, AGUET and DERVILLE, SEIGE, WESTERMAYER, WALTHER, JACKH, DOBROKLOWSKI and ALBRECHT have examined the semen of consumptives who were not suffering either from miliary or genital tuberculosis, with varying results ; their conclusion, therefore, cannot be regarded as clear-cut, but they indicate that as a rule the semen is unaffected, apart from miliary or local lesions in the genital organs. FRIEDMANN, who injected human or bovine tubercle bacilli into the vas deferens of rabbits, found living bacilli in the 7-day-old fœtuses sired by the experimental animal. Injection of bacilli into the testicle gave the same results. Most of the experiments conducted on the foregoing lines, with a view to throwing some light on the problem of transmission of the disease from a tuberculous father to his children, fail to be convincing because the conditions are so far removed from those under which normal insemination is carried out.

As regards the mother, it is possible that transmission of the disease may be effected either by the passage of bacilli from the maternal blood-stream through the placenta, or by infection of the ovum itself, as a result of tuberculous lesions in the genital organs.

Bacteriological research has shown that certain organisms can penetrate the placenta ; the organism responsible for anthrax is one of these (ARLOING, CORNEVIN, THOMAS, STRAUS and CHAMBERLAND, MARCHAND, PALTAUF) ; other examples are the cocco-bacillus of fowl-cholera (STRAUS and CHAMBERLAND, CHAMBRELENT), the *Bacillus typhosus* (NEUHAUSS, CHANTEMESSE and WIDAL, ÉBERTH, ERNST, GAGLIO), the pneumococcus (NETTER), the

streptococcus (CHAMBRELENT and SABRAZES, AUCHE), the glanders bacillus (CADEAC and MALLET, LIEFFLER), the virus of rabies (PERRONCITO and CARITA), and the organism of paludism (BONZIAN).

It seems, however, that the infective agent is arrested in most cases by the placenta which really does act as a barrier to noxious organisms attempting to invade the fœtus. Before this barrier can be penetrated the blood-stream must be heavily laden with micro-organisms, according to the view of the observers mentioned above ; even so, not every species of micro-organism is capable of penetrating the placenta.

The presence of KOCH's bacilli in the blood of tuberculous patients has been demonstrated by many observers, of whom VILLEMEN was the first. His findings were confirmed by THAL and NESTEROW, TOUSSAINT and BAUMGARTEN, even before the organism itself was discovered. Later the bacillus was found in the blood of animals, and in cases of tuberculous bronchopneumonia, by GOSSELIN, JEANNEL, KUSS, GALTIER, MEISELS, RUTIMEYER, LUSTIG, STICKER ; and later by LIEBMANN, BARLING and WILSON, MONKEBERG and VERGARA-KELLER, in ordinary cases of phthisis. Usually, however, cases of phthisis give negative results, according to KOSSEL, PRIOR, EWALD, ABRAHAM, CANTINI, HAMERLE, MICULICZ, GUTTMANN and EHRLICH, and others.

It is possible, and even probable, therefore, that bacilli penetrate the placenta, but, according to the observers quoted above, only in small numbers, except in the case of tuberculous bronchopneumonia. Furthermore, I have already pointed out that post-mortem examination of fœtuses or newly born infants occasionally reveals the presence of tuberculous lesions, proving decisively the possibility of fœtal infection during pregnancy. Examples are not lacking of transmission by this method ; since CONHEIM stated that they were sufficiently rare to be counted

on the fingers of one hand, new cases have come to swell the figure, as shown by the observations of FODERE, HUSSON, RICHARD, FLEURY, KONIG, STIRMANN, ADAM, VERNEUIL, BROCA, DOLBEAU, PADIEU, SCHMORL and KOCKEL, WARTHIN, SARWEY, RUSER, RUBEN, HUTER, POULAILLON, DEMNE, CHARRIN, BERTI, JACOBI, MERKEL, LANNELONGUE, SABRAZES, SABOURAUD, LEHMANN, GARTNER, GEIPEL, BANG, MALVOZ and BROUWIER, BUNGE, CHABRY, DE RIENZY, STOCKEL and others.

Where there are no lesions at birth, it has sometimes been possible to demonstrate the passage of the bacillus from mother to child by the animal-inoculation method; this was done by CHARRIN, of Lyons, in 1873, and later by JOHNE, BIRCH-HIRSCHFELD, LANDOUZY and MARTIN, LAUENBERG, HUGUENIN, LONDE and THIERCELIN, ARMANNI, AVIRAGNET and LAURENT PREFONTAINE, BAR and RENON, and others.

On the other hand, numerous negative results have been recorded of attempts to discover the bacillus, or to demonstrate its presence by inoculation of placental or foetal tissue into animals. Such failures have been reported by HELLER, WEISCHSELBAUM, VERCHERE, CHARRIN and KARTH, KURTJANI, CHAMBRELENT, HUTINEL, VIGNAL, LONDE, SCHMORL and KOCKEL, STRAUS, CORNET and others. As a result, the positive findings came to be regarded as exceptional. BOLOGNESI, who inoculated 130 guinea-pigs and rabbits with placental tissue and blood obtained from the umbilical cord of cases in which the mother was tuberculous, records only two deaths from tuberculosis among the experimental animals. These investigations, as a whole, have led clinicians to conclude that direct, congenital transmission of KOCH's bacillus is quite exceptional, the immense majority of cases of tuberculosis not being attributable to this cause, and consequently depending on postnatal infection.

This opinion, however, is based chiefly on negative

findings and opinions. Inferences drawn from negative facts are not, as a rule, conclusive, since a negative result in an experiment may be due to faulty technique. Failure to discover bacilli in the organs of a foetus, or to infect guinea-pigs by the inoculation of placental blood or tissue, does not prove conclusively that no bacilli were present in these materials; failure may depend on defects of method, or on the fact that few bacilli were distributed throughout the body of the foetus, the bulk of them being localised in some lymphatic gland, which could only have been discovered by chance; moreover, the organisms might have been attenuated, so that their virulence was insufficient to cause typical lesions on inoculation.

This is shown by the fact that BRINDEAU and P. CARTIER, using more accurate methods, were able to demonstrate the presence of the bacillus, by direct examination and by inoculation, 25 times out of 34, using blood from the umbilical cord of a child born of a tuberculous mother; which is equivalent to saying that in more than 76 per cent. of cases the bacillus had succeeded in passing the placenta.¹

Moreover, it is not only the bacillus, in its normal form, which is transmitted from the mother to the foetus; the same organism may be transmitted in the form of a filtrable virus.

The discovery of this virus, and of its almost invariable transmission from mother to child, has seriously embarrassed those authorities who deny the existence of heredity. Since there can be no doubt that such transmission occurs, they must decide whether they will abandon their opinions or go on clinging to them. Must they return to the earlier view, and revolutionise the theory of the pathogenesis of tuberculosis laid down in every textbook, upon which so much subsequent work has been

¹ BRINDEAU and Pierre CARTIER. "Contribution à l'étude de la Tuberculose Héritaire." *Bull. Académie de Médecine*, t. ci, 1929, June 12, p. 772.

based? Are they to admit themselves to be on the wrong track?

Such admissions are encountered all too seldom because the dogmatism of medical teaching has accustomed members of the profession to expect concrete formulæ, in direct opposition to the true scientific outlook which must always be fluid. Such a state of mind does not conduce to the recognition and admission of errors.

A true scientist must always regard his inferences as provisional and be prepared to revise them. HIPPOCRATES taught us this when he wrote in his *Aphorisms*: "To know is science; to think one knows is ignorance."

I cannot help thinking this wise precept ought to be applied here. It has been discovered that infectious elements of tuberculous origin can be transmitted from the blood of a tuberculous mother to the fœtus; this is an excellent opportunity to decide whether a mistake has not been made in rejecting the theory of heredity. In the meantime it is prudent to regard the question as *sub judice*. This has not been the attitude adopted by the supporters of the theory of infection, however; and they have found an ingenious argument to buttress their position by contending that the transmitted elements are of no importance, and that any influence they may have fades soon after birth.

At bottom, what do they know about it?

I hold, on the contrary, that this discovery opens up a new field in the study of the hereditary transmission of tuberculosis; to prove this, however, prolonged experimentation will be necessary, as I shall presently show; I have undertaken some experiments of the kind myself. Until the results of these investigations are available we must be content to consider the facts relating to the filtrable virus, and to discuss the probable bearing the discovery of this agent will have in elucidating some of the problems connected with tuberculosis.

Polymorphism of the Tubercle Bacillus. The Filtrable Virus.

The tubercle bacillus, most commonly known in its acid-fast form, may present widely different appearances, depending on the medium in which it is cultured. It may take the form of cocci which are not acid-fast (MUCH's granules, or VAUDREMER forms), or it may become filamentous, with various intermediate bacillary forms. In the granular form, the elements may be single, or may form diplococci, tetrads or chains. These protean forms of the bacillus were first demonstrated by FERRAN, MUCH, FONTES, KARWAKI, VAUDREMER and others.

Resistance to acids and susceptibility to Gram-staining vary considerably in these different forms of the organism. Although it has been possible to study them *in vitro*, it has not been possible, so far, to detect their presence in the organs of animals once they have lost their resistance to acids, since the small size of the organisms and their scarcity when scattered through an organ, render them easily confused with ordinary cocci in the tissues. *We cannot be sure therefore that, under certain conditions in the human body, the bacillus does not assume some of the transient forms observed in cultures.* It is quite possible that this does occur, and that these are saprophytic forms which may remain latent in the tissues for years, almost without multiplying, until the environment becomes favourable to growth, when the organism resumes its resistance to acids, its powers of proliferating and its pathogenicity.

It is worth noting that tissues endowed with special vitality, more especially embryonic tissues, seem able to depress the activity of the bacillus and reduce it to a saprophytic form devoid of its waxy envelope; at all events this is what the experiments of MAFUCCI, RAVETLLA-PLA, ABADIA and others, seem to indicate. This faculty of embryonic tissues for attenuating organisms which are neither too virulent nor too

abundant, accounts for certain aspects of tuberculosis which have been puzzling hitherto—for example, the rarity of tuberculous lesions in the fœtus, despite the transmission of bacilli from the maternal bloodstream; and the absence, in most cases, of a positive skin reaction in the new-born infant of a tuberculous mother, despite the fact of congenital infection (for the forms of the tubercle bacillus which are not acid-fast only produce tuberculous sensitisation very occasionally); and, finally, it explains the long latent period before the disease becomes active.

FONTES, of Rio de Janeiro, published a paper in 1910, in the *Memoirs of the Oswaldo Cruz Institute*, in which he showed that certain elements of the tubercle bacillus can pass a Berkfeld filter capable of arresting organisms visible microscopically. He found that when the pus from a tuberculous abscess was filtered in this way, the filtrate, when injected into a guinea-pig, caused a slow hypertrophy of the lymphatic glands, and that a few acid-fast bacilli could be isolated from the pulp of such glands.

These memorable experiments were accorded scant credulity by bacteriologists, some of whom tried to confirm FONTES' findings; they probably performed the task carelessly, for they all failed. Thenceforward the filtrable virus was regarded as a myth, and FONTES was accused of faulty technique or the use of defective filters. FONTES abandoned his investigations in disgust, but certain interesting experiments performed by VAUDREMER, and later by HAUDUROY, drew fresh attention to this question; observers with more skill and patience than those who had attacked FONTES repeated his experiments and confirmed his positive findings. Among the earliest of these workers were CALMETTE, VALTIS, NEGRE and BOQUET of the Pasteur Institute, who recognised, in 1925, the accuracy of the work of the Brazilian biologist, published thirteen years previously. Their findings were confirmed by ARLOING and DUFOUT, ARLOING, DUFOUT and MALATRE, DURAND and CHARCHANSKI,

and later by VANUCCI, VERDINA, VASILIU and TRIMONOIU, MELLE, DE BONIS, FLOYD and HARRICK, TORIES and MELLO, TOUGOUNOFF, CANELLI and BASCO, MELLO and JOST, VASCELLARI, Lydia RABINOWITCH, CASSANGRANDI, PARTEARROYO, CAMAROSA, BOCCHINI, VAN BENEDEN and others.

Their conclusions may be summed up as follows :—

(a) The ultra-microscopic virus appears to accompany KOCH's bacillus in whatever medium it is cultured ; its presence has been demonstrated in the filtrates of young cultures grown in glycerine-broth, in tuberculous sputum, in material from caseous lesions, in the sero-fibrinous exudate of tuberculous pleurisy, in the exudate which sometimes occurs following artificial pneumothorax, in the blood of tuberculous patients, in the menstrual lochia of tuberculous patients, and even in the urine of patients with miliary tuberculosis or tuberculous lesions of the kidney.

(b) This filtrable virus, when inoculated into a guinea-pig, causes hypertrophy of the lymphatic glands, especially those at the hilum of the lung. This hypertrophy does not present the characteristic pathological appearance of a tuberculous lesion, although acid-fast cocci or short bacilli are occasionally found in the affected gland.

(c) Animals inoculated with the filtrable virus waste, and in most cases die in a condition of extreme cachexia ; others, after a period of wasting, survive the inoculation.

(d) All inoculated subjects give a positive skin reaction to tuberculin ; this develops fifteen to twenty days after inoculation with the filtrable virus, and ten to twelve days after inoculation with unfiltered tuberculous material. In the guinea-pigs which recover from inoculation with the filtrable virus, the skin reaction ultimately disappears ; whereas, in guinea-pigs inoculated with tuberculous material, apart from certain cases of anergy, the skin reaction persists.

(e) The virulence of the filtrable virus appears

to be increased by passage. If a guinea-pig is inoculated with the virus, and if, later, the hypertrophied glands and certain organs of the animal are crushed and injected into another guinea-pig, characteristic tuberculous lesions are often produced in the second animal.

(f) The filtrable virus, when administered subcutaneously every twenty-five days, gives rise to KOCH's phenomenon; this seems to demonstrate its bacillary origin. (DEBRE, LELONG and BONNET.)

(g) F. ARLOING and DUFOURT showed that if tuberculous filtrates were inoculated into a pregnant guinea-pig the virus could be passed from the mother to the foetus through the placenta.

Young guinea-pigs, born of mothers which have been inoculated with the filtrable virus during pregnancy, seldom die; some of them, however, become marasmic and succumb to a condition recalling the progressive malnutrition described by COUVELAIRE as occurring in the children of tuberculous mothers.

Certain other properties of the filtrable virus are worth recording, notably those demonstrated by the experiments of PARAF, VALTIS, BOQUET and NEGRE, TURBAN, KRAUSE, REICH, ARLOING, THEVENOT, DUFOURT, MALARTRE and others; these observers found that injections of tuberculous filtrates confer a certain power of resistance to tuberculous infection. FLOYD and Margaret BERRICK question their findings, but differences of dosage may explain the discrepancy. The relative immunity likely to be conferred by small doses of the filtrable virus hardly seems to agree with clinical findings.

The glandular hypertrophy may be produced equally well by the injection of filtrates heated to 80° C. for twenty minutes or, indeed, by injecting tuberculin or emulsions of dead tubercle bacilli—that is to say, in the absence of either living bacilli or the filtrable virus. It remains to be shown whether hypertrophied glands produced in this way can produce positive lesions on reinoculation.

The virulence of filtrable virus varies considerably ; F. ARLOING and A. DUFOURT write of it as follows : "Inoculation of filtrates obtained from human tuberculous material can produce various pathogenic lesions, ranging from nodular, caseous, tuberculosis (rarely) or lymphatic involvement with fatal cachexia (the commonest lesion) to a brief, transient condition which is only revealed by a fleeting period of allergy, and disappears as the system destroys the virus."

So far the frequency with which the last condition occurs has not been determined.

From the point of view of heredity, with which we are particularly concerned, the important thing about the filtrable virus is that it is capable of passing through the placenta. That it *can* so pass is now beyond question ; investigations carried out by CALMETTE, VALTIS, COUVELAIRE, LACOMBE, SAENZ, ARLOING and DUFOURT have proved it up to the hilt. The presence of the ultramicroscopic elements of KOCH's bacillus has been demonstrated in the amniotic fluid obtained by hysterectomy from a tuberculous woman. Their presence has also been demonstrated, in nearly every case, in blood obtained from the umbilical cord of infants born of tuberculous mothers.

When it is realised that the bacillus, in its normal acid-fast form, can be isolated, in 76 per cent. of cases, from blood obtained from the umbilical cord in tuberculous lying-in cases, as BRINDEAU and CARTIER, using improved technique, were able to show ; that the presence of the filtrable virus can be demonstrated in blood from the same source 90 times out of 100 ; and that parents transmit certain characteristic properties of their body fluids to their children (for example specific complement deviation)—can it be maintained that heredity plays no part in the transmission of tuberculosis ? Can it be contended that KOCH's bacillus, the filtrable virus, or the specific properties of the body fluids which are inherent in the infant at birth, count for nothing in the ætiology of the disease, but are entirely negligible ? In my view,

such a contention is unwarrantable, if not completely erroneous.

The only objections of any value put forward against these facts were accurately summed up by Leon BERNARD, when he wrote : " Although the presence of bacilli in the viscera of certain infants cannot be disputed, as CALMETTE, VALTIS and LACOMBE have shown, no casual relationship has been demonstrated between the presence of these organisms and the deaths of the infants."

Still less, however, is there any proof to the contrary. Although there is nothing to show that the infants in question were actually the victims of tuberculous heredity, I have already quoted examples in which the influence of heredity was unquestionable. These include cases in which the infant shows more or less extensive tuberculous lesions at birth ; such cases of congenital tuberculosis are seldom found, however, because the necessary post-mortem examination is seldom carried out on fœtuses, and is rarely performed on infants before any chance of infection could have occurred. There are other cases of fatal hereditary transmission of the disease which appear to be genuine—those cases in which the infant, although it is taken from its parents at birth and reared with the most elaborate precautions against infection, nevertheless succumbs to tuberculosis. In any case, how can it be pretended that the presence of living tubercle bacilli in the system is of no consequence, when all the experimental evidence goes to prove the contrary?

Even disregarding the acid-fast bacillus, which in its normal form frequently succeeds in penetrating the placenta, the opponents of the theory of heredity contend that the filtrable virus plays no part in the transmission of tuberculosis, on the ground that among guinea-pigs inoculated with the virus, a certain number survive without appearing to suffer from anything more serious than a temporary wasting. What of those which die, and which, in some cases, are found to have typical tuberculous lesions? Not

every child to whom the disease has been transmitted congenitally dies of tuberculosis, and the same is true of guinea-pigs inoculated with the filtrable virus.

Moreover, the experimental results obtained by inoculation and those which follow congenital transmission of the disease are not entirely comparable. In one case the filtrable virus is injected subcutaneously in a single dose, while in the other the foetus receives tubercle bacilli—in small numbers, it is true—into its blood-stream for months on end, as well as a certain amount of the filtrable virus. No strict parallel can therefore be drawn between the two phenomena.

* * * * *

Moreover, an argument is to be found in the chronic form of tuberculosis common in man, which I believe to have an important bearing on the theory of heredity.

The Significance of Human Tuberculosis of the Chronic Type.

I have put forward the suggestion that the chronic type of tuberculosis, which is the common type, and more or less amenable to treatment, is the outcome of congenital transmission of the disease to the subject in the form of the filtrable virus or a saprophytic organism, rendered temporarily innocuous by the embryonic tissues; I ascribed the long latent period to the delay necessary to convert the modified form of the organism into pathogenic bacilli.

Prof. CALMETTE points out that this is merely a hypothesis, which I readily admit to be the case; but is it not also a hypothesis to assert that infection always occurs postnatally? If my reasoning with regard to chronic tuberculosis is followed closely I believe that a fact emerges which will enable the reader to decide between the two hypotheses.

The acid-fast bacillus—which is regarded as the infective agent, and which is, in point of fact, the only

form of the organism likely to transmit the disease by infection, since it is the only one disseminated by consumptives—is incapable of producing, in animals, the chronic type of disease which is characteristic of human tuberculosis.

To this fact my opponent replies that when extremely small doses of bacilli are administered to guinea-pigs a chronic form of tuberculosis is produced which takes a year or more to develop; considering that guinea-pigs are short-lived animals the time taken by the disease to develop and produce a fatal termination corresponds approximately to the average course of the disease in human subjects.

It is true that the course of the disease in animals is much slower when tubercle bacilli are inoculated in minimal doses; but from the moment at which infection actually occurs the disease follows a progressive unalterable course. This bears no resemblance to chronic human tuberculosis, which may persist for years without giving any trouble, and without progressing, and which, moreover, gives rise to variable symptomatology and is frequently regressive and even curable.

It has never been possible, by means of the acid-fast bacillus, to reproduce the human type of the disease in animals, whatever their species, breed, age or sex, whatever the dosage or the method of inoculation used; no latent period has ever been observed following infection; osseous, synovial, articular and cutaneous forms of the disease, which are common in man, have never been seen in animals; periods of arrest and regression are never seen, and no cases of cure are recorded in animals inoculated with the normal, acid-fast bacillus.

I should not be inclined, therefore, to use the term “chronic tuberculosis” for the slowly progressive type of the disease produced in guinea-pigs by the administration of minimal doses of acid-fast bacilli; chronic human tuberculosis differs from this condition in its latent period, its symptomatology, its irregular and often regressive course and its curability.

Whatever method of administration is used, the acid-fast bacillus is incapable of reproducing in animals the common form of human tuberculosis.

Has the bacillus this property in man alone? Do all animals react to the bacillus in one way while man, and man only, reacts in a different way? That would certainly be remarkable. But the explanation has been suggested—indeed, almost proved—by experiment.

MAFUCCI, BAUMGARTEN, and later PAISSEAU and OUMANSKY, have shown that the human form of tuberculosis with all its characteristics can be produced without difficulty in animals, either by *infecting embryos*, or by inoculating it with filtrable virus or with the saprophytic forms of the bacillus. The conclusion seems to be that the chronic, regressive and curable form of tuberculosis, in animals as well as man, is the result of prenatal infection, either with the acid-fast bacillus itself, or with the filtrable virus or saprophytic forms of the organism.

Moreover, in infants infected after birth the disease runs a rapid, progressive and fatal course. The infants infected by the Neuenberg midwife died of tuberculosis within fourteen months. Those infected at Lubeck were doomed in the same way.

In considering the experiments discussed in this chapter it must be recognised that they differ from those designed to prove the occurrence of infection, in which the variable factors, such as age, species, environment, habits and food, were many, and exercised an influence on the results obtained. In the experiments considered in this chapter such extraneous factors as species, breed, environment, habits, food, dosage and experimental methods are of no account; the paramount factors are the form of the organism, and its transmission to the embryo.

The acid-fast bacillus will never produce the chronic, regressive, curable type of tuberculosis in animals. The saprophytic form of the bacillus or the filtrable virus, or even the normal form of the bacillus, if

injected into the embryo, will give rise to the chronic type of tuberculosis which is common in man.

The conclusion almost seems to be forced upon us. Who can fail to be struck by the essential difference between the accepted theory of postnatal infection and my own theory of prenatal transmission? The reading of the facts which I have set out, depending as it does on the comparison between the human type of the disease and the experimental type, is fundamental: it clearly discredits the accepted theory and confirms the view of which I am a supporter. The accepted theory fails to fit in with the facts, whereas the theory of heredity covers them. I consider the experimental findings discussed in this chapter to be the chief argument in support of the theory of tuberculous heredity.

CHAPTER VIII.

THE AGE-INCIDENCE OF TUBERCULOSIS.

Pathogenic and Ætiological Classification.

IN investigating the mortality from tuberculosis according to age, I shall be raising a question which is often neglected, yet which has an important bearing on the ætiology of the disease. For this purpose I must refer again to the statistics showing the death-rate in Lyons between the years 1906 and 1925, which I have discussed in a previous chapter.

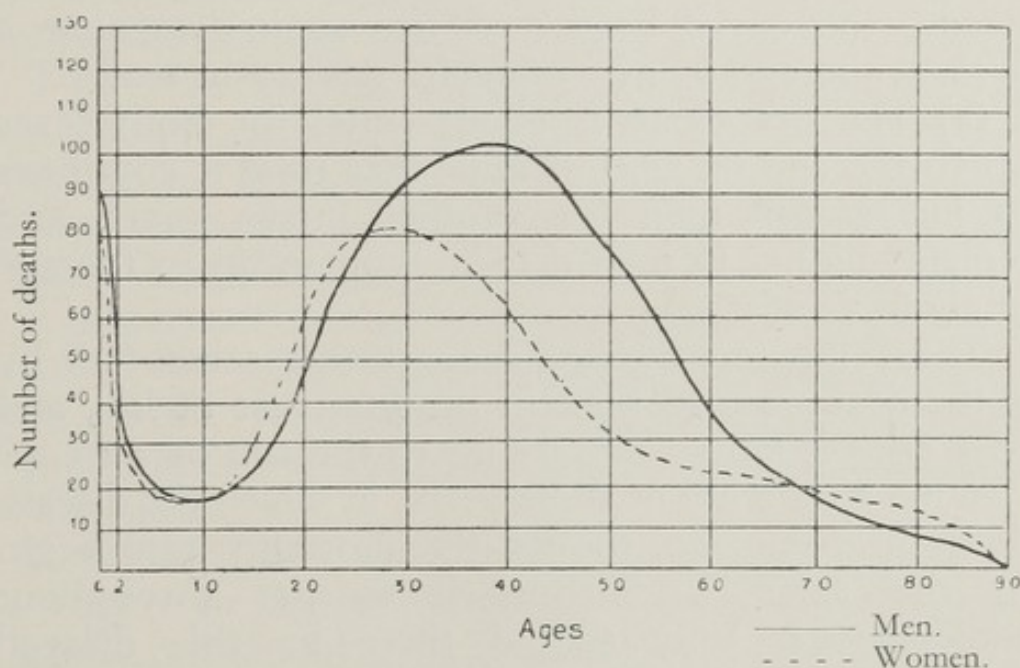


FIG. 31.—The mortality rate from tuberculosis in 100,000 inhabitants; for the years 1906-1925 inclusive. Calculated according to age and sex.

After an examination of 188,124 death certificates issued during that period, curves were plotted, each of which covered a period of ten years; they gave some idea of the distribution of deaths according to sex and age, but were inaccurate as regards the first year of life, since only the average death-rate between birth and ten years was considered, and the mortality

from tuberculosis fluctuates considerably during these early years. Since the original curves took no account of this fact I was forced to revise them, paying particular attention to the yearly fluctuations in the death-rate occurring before the tenth year of life.

Fig. 31 gives the corrected curves, and offers some points of interest.

(1) To begin with, there is a comparatively high death-rate during the first two years of life, and especially during the first year; this rate, however, decreases considerably from year to year, up to about the tenth year, the decline being rapid in the first two or three years, and most marked in the year following birth.

(2) After a period, between the ages of 7 and 12, during which the rate is low and comparatively steady, the curve begins to rise again, reaching a peak at the age of 25 in females and 40 in males.

(3) The death-rate is about equal for both sexes up to the age of 25, but after that time it continues to increase in men for another fifteen years, and remains higher in men than in women up to the age of about 70 years.

The following queries suggest themselves: Why is the death-rate so high in the first year of life, and why does it fall so rapidly up to the age of 3 or 4?

Why, after a lull of some years, in which the disease does little damage, should the mortality rate begin to rise again, and continue to rise throughout adolescence? Why should there be this delayed development of tuberculosis?

Lastly, why should the sexes be unequally affected?

It is no question of small variations in the death-rate, which might be explained by differences of conditions or environment; the differences involved are considerable and must have definite and distinct causes. To attempt to account for these differences by the theory of infection is hopeless. If infection plays any part, as it certainly does during early infancy, it must be only one of several factors; that there are

other factors involved is indicated by the curves, and these factors are of primary importance.

It can scarcely be supposed that tuberculosis is infectious during the first year of life, that it ceases to be infectious until the beginning of adolescence, when it resumes its infectivity only to lose it again later; nor can it be assumed that infection follows the same course in both sexes up to the age of 25, and after that affects males more frequently than females.

There must be some reason for the variations in the incidence of the disease, and this will have to be discovered if any progress is to be made in our study of the ætiology of tuberculosis and its prophylaxis.

(1) Let us consider the first point, namely, the high incidence of the disease at birth, and its rapid decline during the first few years.

Two theories are available: either the infant is congenitally affected, or else it becomes infected after birth. If the child has the organisms in its body at birth the disease will develop at once, or will already have begun to develop *in utero*, and death will supervene within a few months. This would account for a maximum death-rate during the first year of life, followed by a rapid decline, and the hypothesis fits in perfectly with the facts as illustrated in the curve.

If, on the other hand, infection occurs postnatally, in order to fit in with the facts illustrated in the curve, it would have to take place immediately after delivery; whereas it would have to occur less readily as time went on. If tuberculosis is as infectious between the ages of 2 and 5 as during the first year there is no reason why the death-rate should decrease so rapidly up to the fifth year.

Consequently, there must be certain conditions favouring the development of tuberculosis which exist before or immediately after birth, but which exert a waning influence as the subject advances in age.

When we recall that the recent investigations of BRINDEAU and P. CARTIER showed that the bacillus

in its acid-fast form could be recovered from the blood of the umbilical cord in 76 per cent. of lying-in cases in which the mother was consumptive, we may take it that congenital transmission of the organism is by no means uncommon, but the rule in three cases out of four.

Nor does there seem to be any doubt that infection of the infant immediately after birth is a common occurrence. The two methods of transmission, therefore, combine to give the curve shown above. Can we form any idea of the relative importance of these two processes? The question is a thorny one, but I shall try to throw some light upon it.

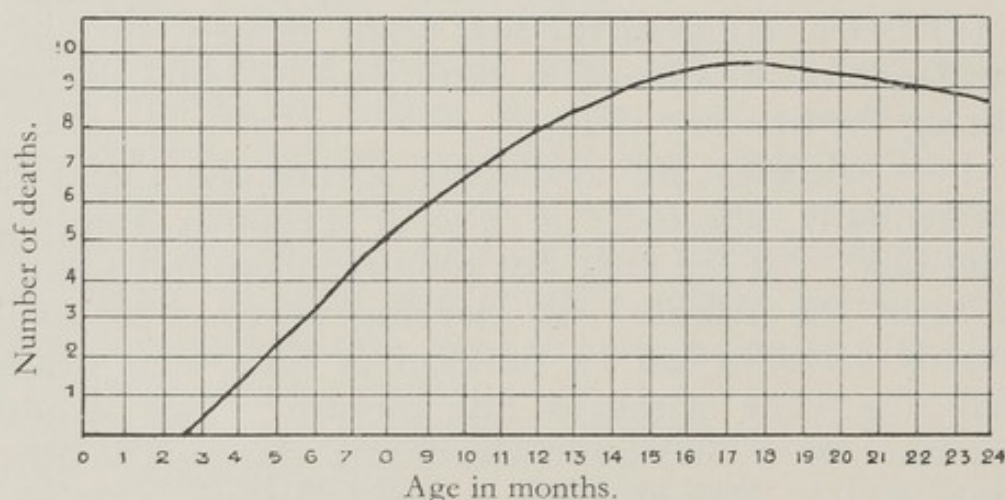


FIG. 32.—Hypothetical curve showing the mortality which might be expected from tuberculosis during the first two years of life, if postnatal infection was the only method of transmission of the disease.

If infection occurs postnatally, it can take place, of course, from the moment of birth onwards, but the chances will increase the longer the infant remains in contact with tuberculous persons; infection on the first day of life will therefore be rare, infection during the first week will be commoner, and during the first few months infection will be frequent. It takes some time, however, for the disease to develop, so that death will rarely occur before a few months have elapsed.

If we consider infection alone, the curve showing the mortality rate would not begin before the third or fourth month, and would then rise for about a year. I have reproduced such a hypothetical curve in fig. 32.

The facts, as obtained from statistics, do not bear out this hypothesis. Fig. 33 represents the actual death-rate from birth to two years.

From this discussion it will be seen that the two factors, infection and heredity, both influence the mortality rate during early infancy, and it is impossible to determine exactly the responsibility which must be ascribed to each.

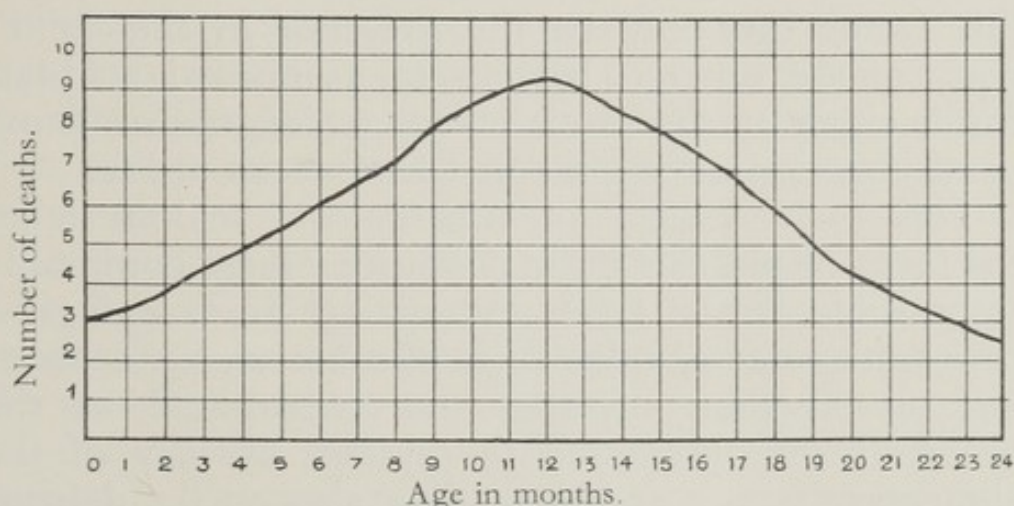


FIG. 33.—Actual death-rate from tuberculosis during the first two years of life.

It appears to be certain, however, that congenital tuberculosis is not uncommon, as has been contended; the disease does not cause death in a few days—it takes a few months at least—so that the patients who die in the first few days or weeks of life can only have been infected congenitally.

Moreover, it is towards the end of pregnancy that organisms pass most readily into the body of the foetus; for it is during the latter part of pregnancy that the placental filter becomes least efficient, owing to its greatly increased area and the large volume of blood circulating through it. It is therefore legitimate to conclude that, in most cases, infection *in utero* occurs towards the end of pregnancy. Since it takes some time for lesions to develop sufficiently to cause death, the commonest type of congenital tuberculosis can only produce a fatal result some months after the birth of the infant. From the foregoing discussion

we may conclude that congenital tuberculosis plays an important part as a cause of mortality among young infants.

We can, therefore, already account for the first peculiarity noted in the curve (fig. 31), namely, the high mortality during the first year of life, and the rapid decline during the ensuing years. The factor responsible for death during the early months of life must exist at birth or immediately afterwards, and this factor can only be the presence in the child's body of the tubercle bacillus in its normal, acid-fast form, either as the result of congenital transmission, or of infection during the first few weeks of life.

This early variety of tuberculosis seldom takes the form of phthisis; the conditions most commonly responsible for a fatal termination are meningitis, peritonitis or some other form of tuberculosis, depending on whether infection was transmitted to the blood-stream or entered the system by way of the alimentary tract; and depending also on the defence offered by the mucous membrane of the intestine and lymphatic glands in these early months of life.

* * * * *

After the period of relative immunity enjoyed by young subjects from the end of infancy to the beginning of adolescence—during which tuberculosis seems to have little effect—a rapid increase occurs in the incidence of the disease, beginning a few years after puberty, and lasting from the age of 15 to the age of 25 in women, and up to the age of 45 in men.

What is the cause of this delayed development of the disease? The variety *which appears during these age-periods is far more deadly than the variety common in early infancy, and is responsible for three-quarters of the total number of deaths from tuberculosis.*

Infection cannot be implicated in these cases, at all events during the months preceding the development of the disease, for symptoms often appear in subjects who have not been exposed to any particular

source of infection. On the other hand, in many cases, where the patient comes of tuberculous stock and has consequently been subjected to the strictest possible precautions against infection all his life, symptoms of the disease will suddenly supervene. As we have seen, infection, in adolescent or adult persons who do not come of tuberculous stock, is exceptional. This delayed form of tuberculosis, in short, attacks those who are predisposed to the disease or who have contracted it immediately after birth. Are they merely predisposed to tuberculosis? Or do they carry latent organisms in their tissues, which become active and multiply when the critical age is reached?

In support of the latter view we may recall the fact that the delayed, regressive, curable variety of tuberculosis is never seen in animals inoculated with the acid-fast bacillus after birth, but that this variety of the disease can be produced by infecting the embryo. PAISSEAU and OUMANSKY reproduced the human type of scrofula in guinea-pigs by inoculating them with the filtrable virus.¹

It may be maintained that the appearance of the disease during adolescence is due to a lack of resistance caused by sexual development and perhaps by sexual excess; but this theoretical argument is unsatisfactory, since the period of maximum severity of the disease—round about the age of 25 in women and between 40 and 50 in men—occurs when the difficulties of puberty are long past. As far as sexual excess is concerned, it may be noted that the period of maximum severity of the disease is the same in monks and nuns as in other members of the community, so that the suggestion does not hold water. Moreover, if the family history is investigated with sufficient care, it is nearly always possible to find indications of the disease in the parents. Heredity always appears to

¹ V. OUMANSKY. "Adénites bacillifères curables; unique manifestation de la tuberculose expérimentale du cobaye." *Thèse de Paris*, 1910. Jouve and Co., Publishers.

outweigh any other factors which may be implicated in the causation of tuberculosis.

I think the following explanation fits in with all the facts, but in setting it down I do not pretend that it is proven, but only offer it as the most likely hypothesis. It has already been shown that 90 per cent. of children born of consumptive mothers are infected congenitally with the filtrable virus. When this virus is inoculated into animals, hypertrophy of the lymphatic glands occurs, and after a time a few acid-fast bacilli may be found in the glands involved; if material from the glands is inoculated into another animal, the tubercle bacillus recovers its normal morphology and virulence.

Why should not events follow the same course in man? Congenitally infected with the filtrable virus, the infant at first develops only a hypertrophy of the lymphatic glands, which may be more or less marked, and is a common condition in infancy. The harmful elements must frequently be destroyed in the glands, or eliminated by diapedesis; but in some cases the organisms may multiply, fostered by a favourable condition of the tissue fluids or by an insufficiency of macrophages. The hypertrophied gland will then become caseous, or in some cases will allow the bacterial elements to be disseminated throughout the body and arrested in another set of glands, where they may form a fresh lesion. In this way, as the lesions progress, the organisms may be disseminated at intervals, and the condition evolve slowly. At each stage the virulence may increase, until eventually a point is reached at which the condition corresponds to invasion by a normal bacillus; this will be the point at which symptoms of active disease become manifest, following years of latent preparation.

MAFUCCI's experiments on the infection of hen's eggs, which were followed up by the experiments of BAUMGARTEN, WEBER and BOFINGER, MILCHNER, Max KOCH and Lydia RABINOWITSCH, showed the influence exercised by the embryo on the form and

properties of the tubercle bacillus. Their findings fit in well with my theory of the causes of the delayed development of tuberculosis. These observers found that when tubercle bacilli were inoculated into hen's eggs, at various stages of incubation, most of the eggs failed to attain full development. The chicks hatched from the remaining eggs nearly all died of tuberculosis, with characteristic lesions, within three months. Considerable interest attaches to the few which survived, since some of them succeeded in destroying the bacilli with which they were infected (a thing which chickens hatched from sound eggs, and subsequently inoculated, are never able to do); while others, after a latent period during which the bacilli remained inactive, developed a delayed variety of tuberculosis with a tendency towards recovery in some cases; this latter type of the disease is never produced when the chick is inoculated after hatching, even with minimal doses of bacilli.

The organism inoculated into the egg becomes, as it were, disintegrated into fine granules. It may be concluded from these observations that the embryonic tissues, endowed as they are with high vitality, modify the form and properties of the bacillus, converting it to the saprophytic form which may remain quiescent for a time and produce no symptoms.

The foregoing experiments confirm my view of the cause of the delayed development of human tuberculosis.

(3) The discrepancy in the death-rates in the two sexes still remains to be explained; it may depend on several factors, but after thorough investigation I have come to the conclusion that the most important of these is alcoholism.

A clear idea of the reasons why tuberculosis takes such grave toll of men of mature age is essential from the point of view of prophylaxis, and I have thought fit to devote a special chapter to this question.

CHAPTER IX.

STATISTICAL INFORMATION : ALCOHOL AND TUBERCULOSIS.

A. General Considerations.

IN considering the statistics relating to deaths from tuberculosis in Lyons, between the years 1906 and 1925, I drew attention to the fact that out of the 188,124 deaths registered during that period the cause noted in the death-certificate was not sufficiently explicit in 28,509 cases. The number of deaths from ascertained causes was therefore reduced to 159,615.

In order to compare the fluctuations of the general death-rate with those of the mortality from tuberculosis it is essential to consider equal numbers of deaths from each cause.

The population of Lyons increased considerably over the twenty-year period under review, as the following census returns will show :—

1906	472,114	inhabitants
1911	523,796	„
1921	561,592	„
1926	570,840	„

The yearly increment in population may be taken as being regular since, apart from the War, no accident occurred to interfere with its progress ; so that we can estimate approximately the number of inhabitants during any given year, and it will be an easy matter to calculate the annual total mortality and the annual mortality from tuberculosis per 100,000 population.

The following table gives the result of this calculation :—

NUMBERS OF DEATHS FROM TUBERCULOSIS COMPARED WITH
NUMBERS OF DEATHS FROM ALL CAUSES.

Years	Number of inhabitants	Total number of deaths	Deaths per 100,000 inhabitants	Deaths from tuberculosis	Deaths from tuberculosis per 100,000 inhabitants	Per cent.
1906	472,114	8,927	1,893	2,251	477	25·21
1907	482,452	8,700	1,805	2,183	452	25·09
1908	492,786	8,267	1,680	2,028	412	24·51
1909	503,122	8,435	1,676	1,847	367	21·89
1910	513,458	7,487	1,459	1,881	366	25·12
1911	523,796	7,915	1,513	1,836	351	23·19
1912	527,596	7,535	1,429	1,758	333	23·33
1913	531,395	7,722	1,454	1,752	329	22·69
1914	535,195	8,592	1,606	1,800	338	20·94
1915	538,995	7,274	1,352	1,697	315	25·33
1916	542,494	7,302	1,347	1,676	309	22·95
1917	546,294	6,828	1,250	1,685	308	24·67
1918	550,094	11,653	2,118	1,913	347	16·41
1919	553,893	7,867	1,422	1,591	287	20·22
1920	557,693	7,987	1,434	1,336	239	16·72
1921	561,592	7,880	1,405	1,410	251	17·89
1922	563,441	7,438	1,321	1,464	260	19·68
1923	565,290	6,800	1,203	1,342	237	19·73
1924	567,139	7,598	1,340	1,472	259	19·37
1925	568,988	7,410	1,305	1,552	283	20·90
1926	570,340					
Totals and average..		159,615	1,500	34,474	325	21·59 (average)

In figs. 34 and 35 the same information is expressed in the form of graphs, one of which illustrates a comparison between the number of deaths from tuberculosis and the number of deaths from all causes, and the other the variations in the mortality from tuberculosis per 100,000 inhabitants between 1906 and 1925.

In fig. 36, furthermore, are shown the fluctuations in the death-rate from tuberculosis, reckoned as a percentage of the total death-rate, over the same period.

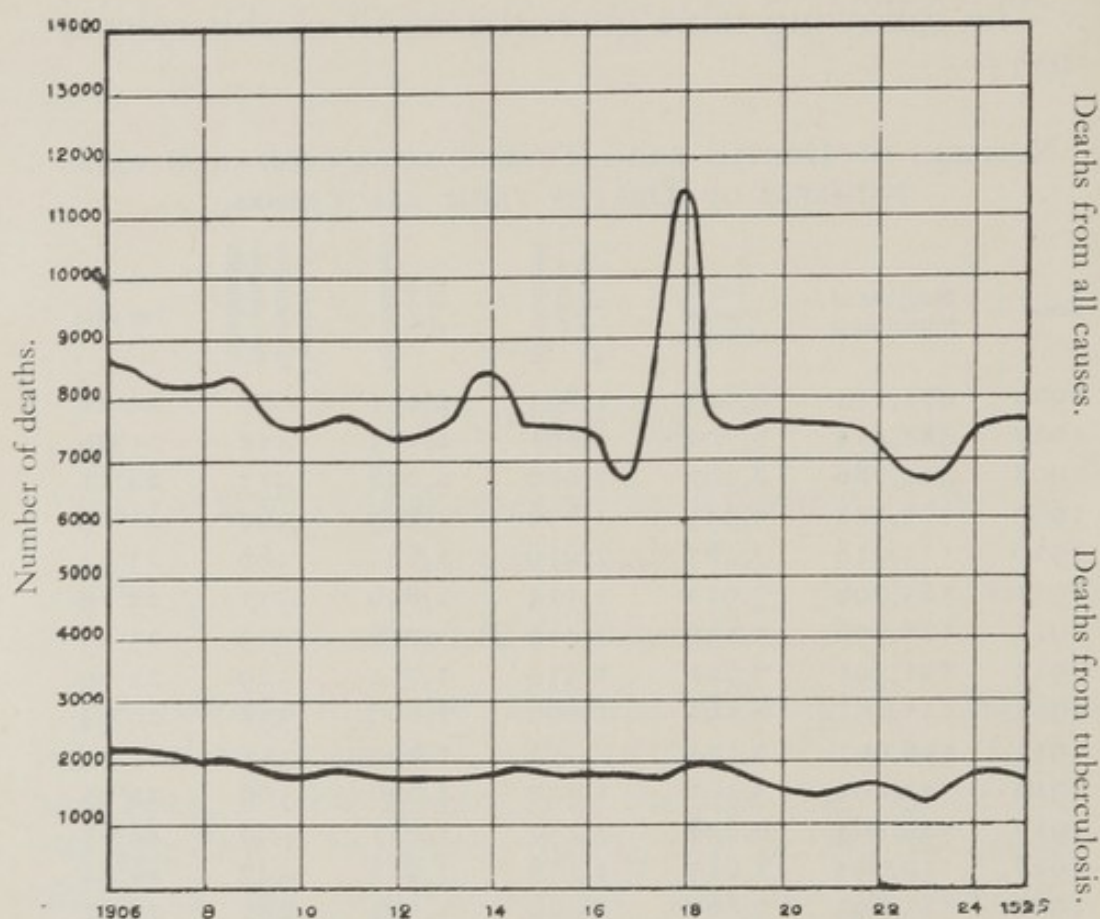


FIG. 34.—Deaths from tuberculosis as compared with deaths from all causes in Lyons from 1906 to 1925.

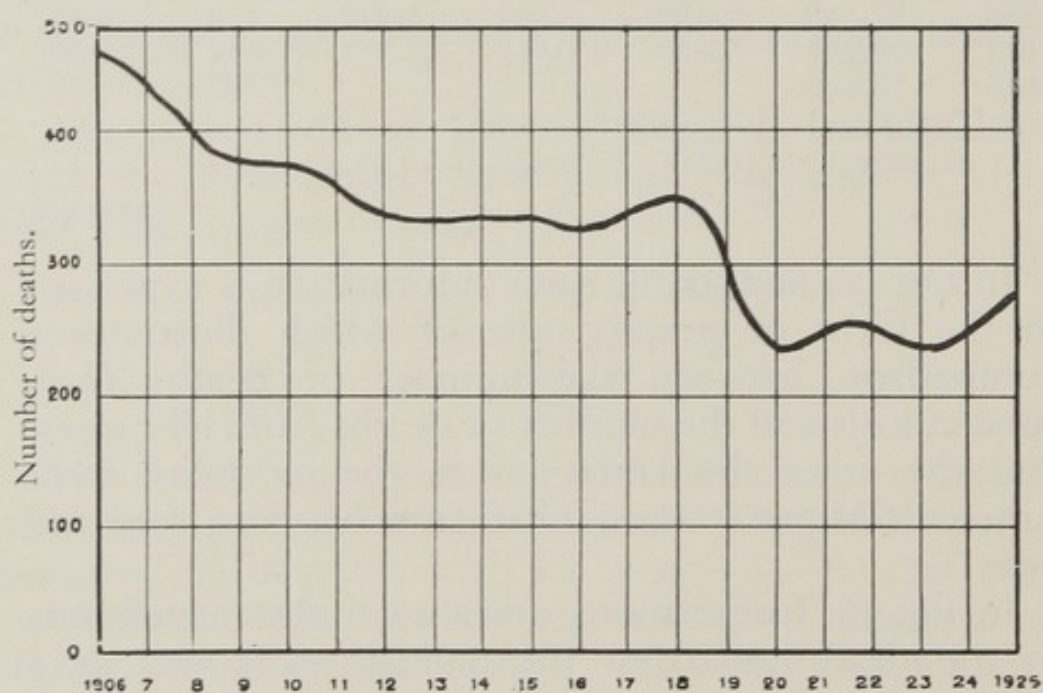


FIG. 35.—Variations in the mortality from tuberculosis per 100,000 inhabitants in Lyons from 1906 to 1925.

These graphs indicate that the general death-rate declined during the years under review, and that the death-rate from tuberculosis also declined within limits. In 1906 there were 477 deaths from tuberculosis per 100,000 inhabitants, whereas in 1920 there were 239, and in 1923 only 237; this progressive

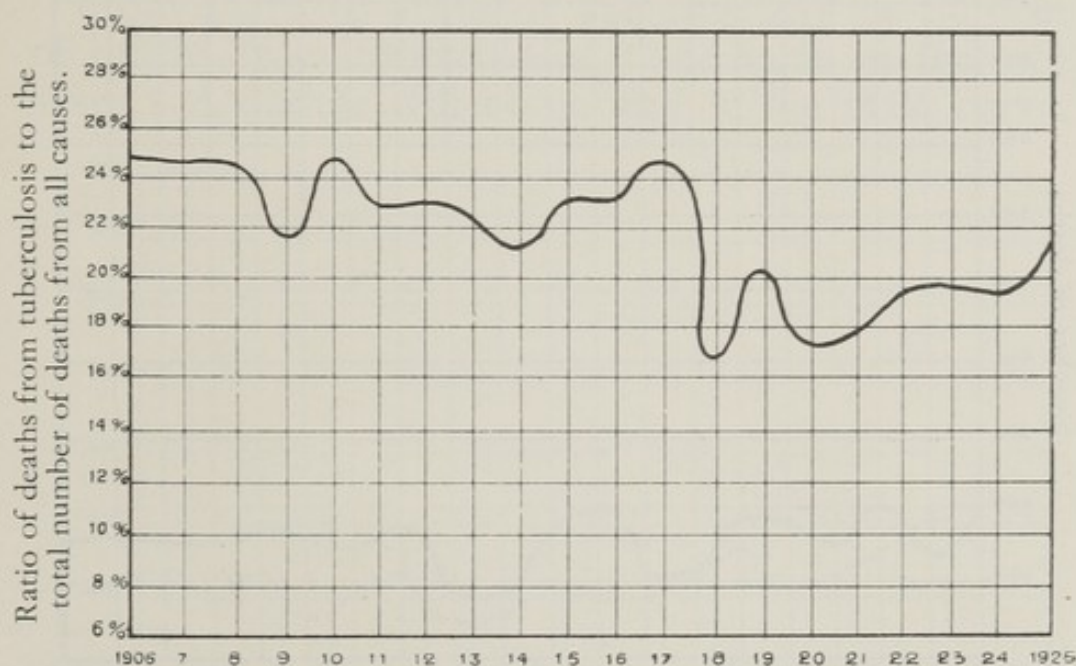


FIG. 36.—Fluctuations in the death-rate from tuberculosis reckoned a percentage of the total number of deaths from all causes; Lyons, from 1906 to 1925.

improvement was not maintained, however, and for some years the proportion of deaths due to tuberculosis has been gradually increasing, until it reached 273 per 100,000 in 1925, and appears to have increased still further since then.

B. *Mortality according to Age and Sex.*

I shall now consider a somewhat peculiar feature of these statistics, which is only apparent when the deaths from tuberculosis are classified according to age and sex.

Figs. 37 to 45 illustrate, in series, the death-rate for each sex at different age-periods, fig. 37 covers the first two years of life, fig. 38 the period from 3 to 10, and each of the remaining figures covers a subsequent ten-year period.

During the first two years of life deaths of male infants are slightly in excess of deaths of female infants, but the curves remain almost parallel throughout the twenty-year period under review. The

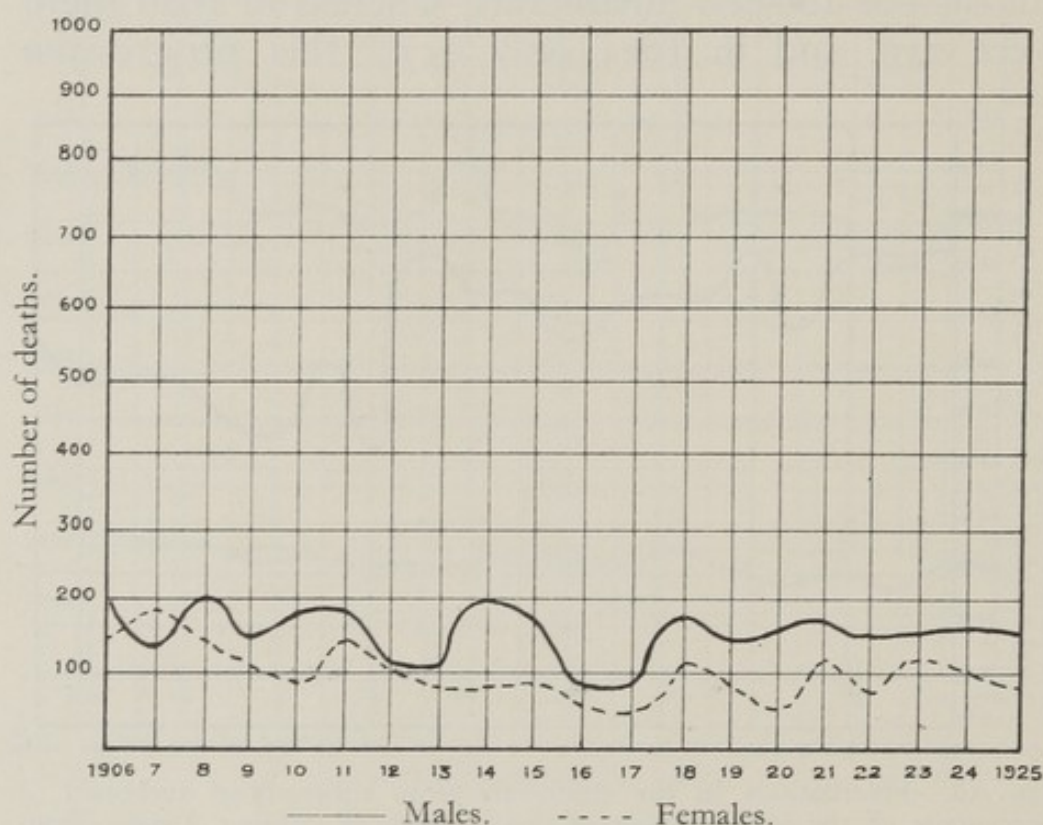


FIG. 37.—Mortality from tuberculosis per 100,000 inhabitants; for the years 1906 to 1925 inclusive. Comparison between the two sexes during the first two years of life.

decrease in deaths in 1916 and 1917 (fig. 37) corresponds to a decrease in the number of births registered during the early part of the War. The following table indicates the extent of this decrease :—

Year	Births registered		Year	Births registered	
1911	..	8,067	1915	..	5,491
1912	..	8,205	1916	..	5,286
1913	..	8,293	1917	..	6,121
1914	..	8,466	1918	..	6,964

During the next age-period—that is to say from 3 to 10 years of age inclusive (fig. 38)—the death-rates in the two sexes show a remarkable similarity. The curve falls considerably in 1918, and does not appear to rise again; the decline in the number of deaths

which it indicates can no doubt be attributed to the beneficent work of the child welfare societies.

Between 11 and 20 years of age (fig. 39) more girls die from tuberculosis than boys. The influenza epidemic of 1918 took greater toll of women in this age-period than of men.

From 21 to 30 years of age (fig. 40) the number of deaths from tuberculosis is the same in the two sexes. A decline will be noticed in the male curve,

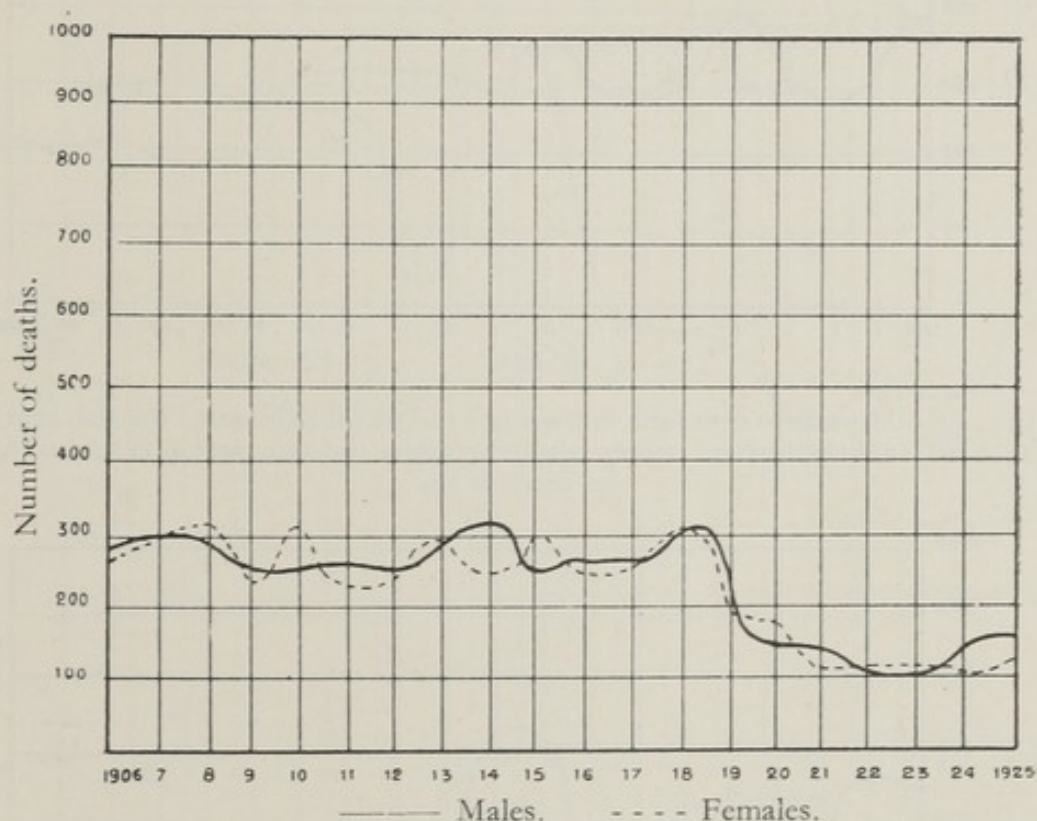


FIG. 38.—Mortality from tuberculosis per 100,000 inhabitants; for the years 1906 to 1925 inclusive. Comparison between the two sexes, from 3 to 10 years of age.

however, between the years 1916 and 1921, showing that the number of deaths from tuberculosis among men decreased during that period; in 1921 the balance was restored and the rates in the two sexes again became similar.

Between 31 and 40 years of age the numbers of deaths from tuberculosis in males and females differ considerably (fig. 41). The death-rate in women begins to show a decline, but in men it increases; in the latter years of the War, however, and those

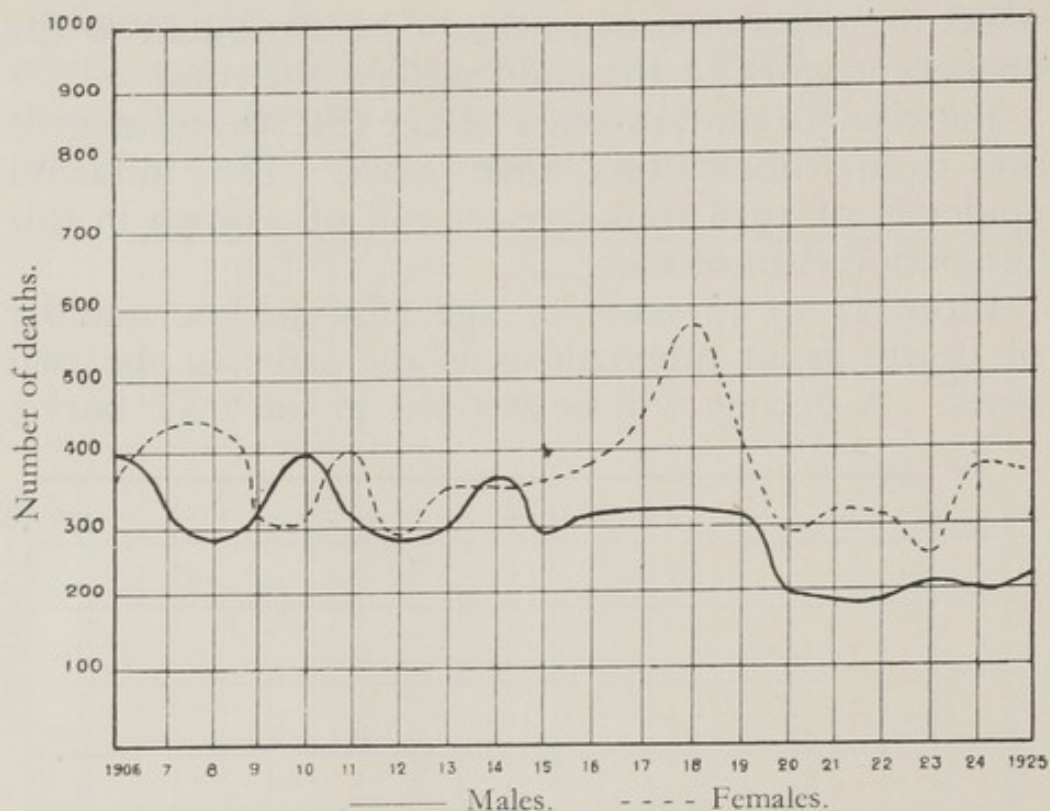


FIG. 39.—Mortality from tuberculosis per 100,000 inhabitants; for the years 1906 to 1925 inclusive. Comparison between the two sexes, from 11 to 20 years of age.

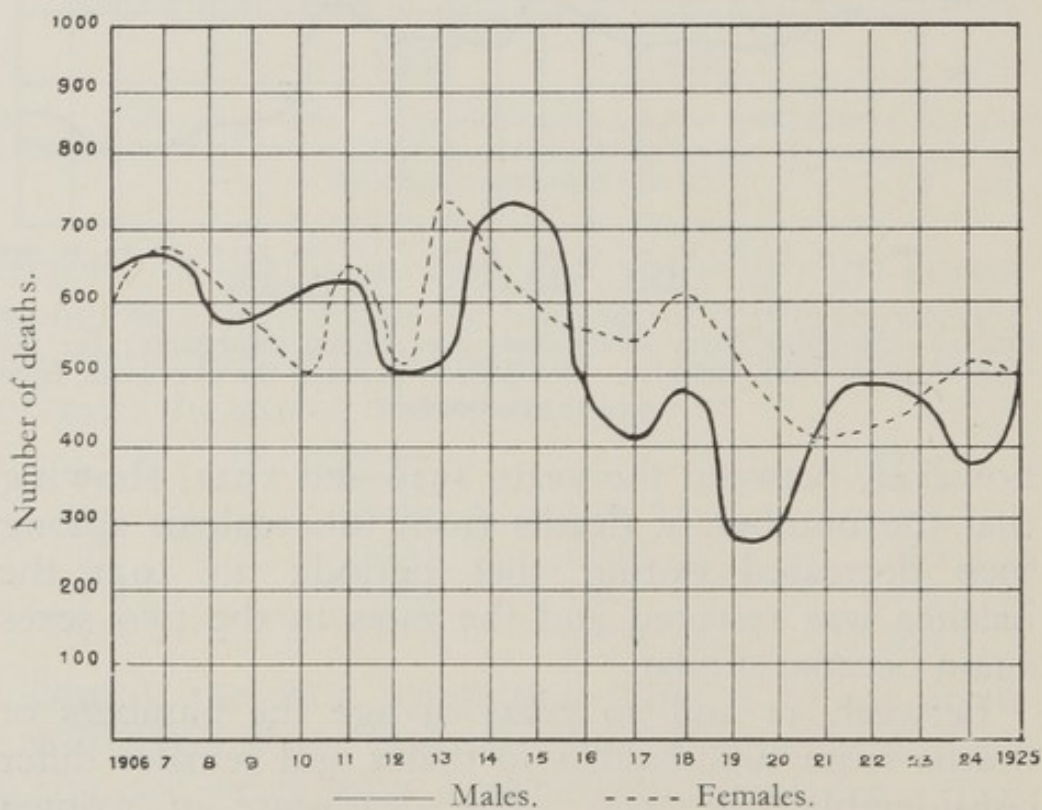


FIG. 40.—Mortality from tuberculosis per 100,000 inhabitants; for the years 1906 to 1925 inclusive. Comparison between the two sexes, from 21 to 30 years of age.

immediately following—that is to say, from 1916 to 1923—the male curve showed a drop, but in 1924 the numbers rose again, male deaths once more becoming greatly in excess of female deaths.

Between 41 and 50 years of age (fig. 42) the death-rate in women shows a marked decline, whereas in men it continues to increase and reaches its maximum; the difference between the death-rates in the two sexes is considerable at that point, the mortality among

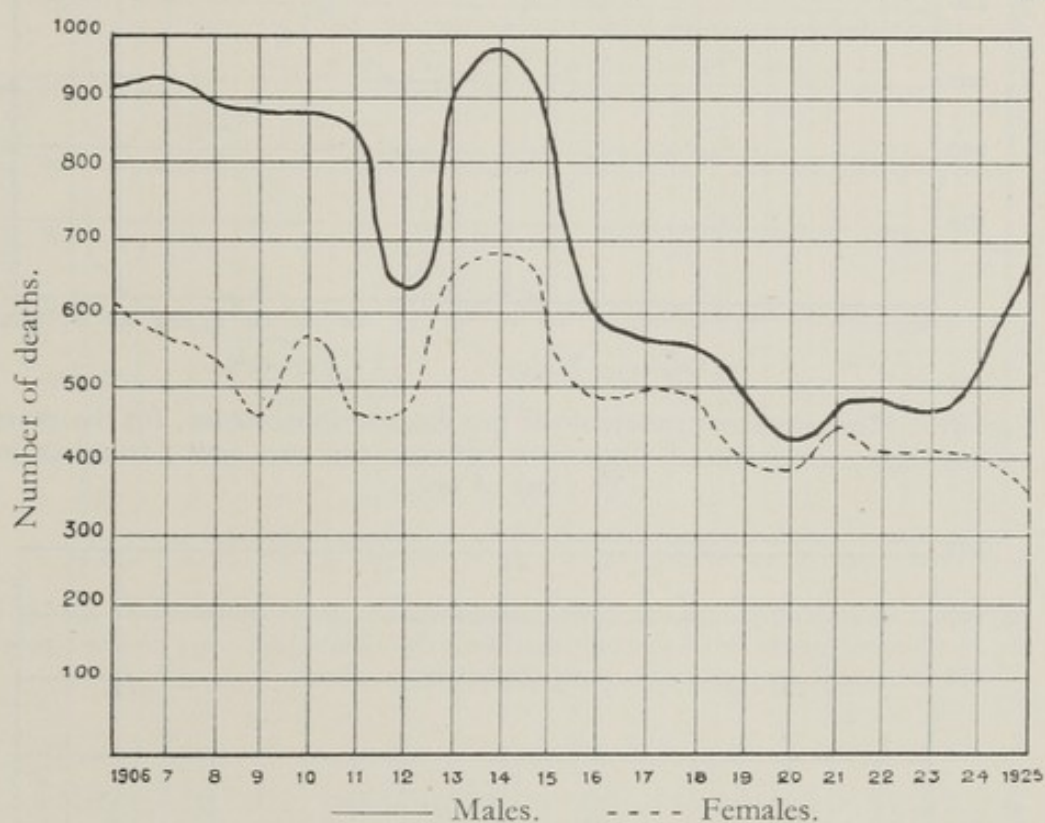


FIG. 41.—Mortality from tuberculosis per 100,000 inhabitants; for the years 1906 to 1925 inclusive. Comparison between the two sexes from 31 to 40 years of age.

men being nearly double that among women. The influence of the War can be traced in this curve, too, but is less marked than in the preceding curve.

From 51 to 60 the disproportion between the two sexes still holds, the men showing nearly twice as many deaths as the women. The War and the influenza epidemic exercise no influence on this curve (fig. 43).

Between 61 and 70 (fig. 44) the curves showing the death-rate in the two sexes tend to approach

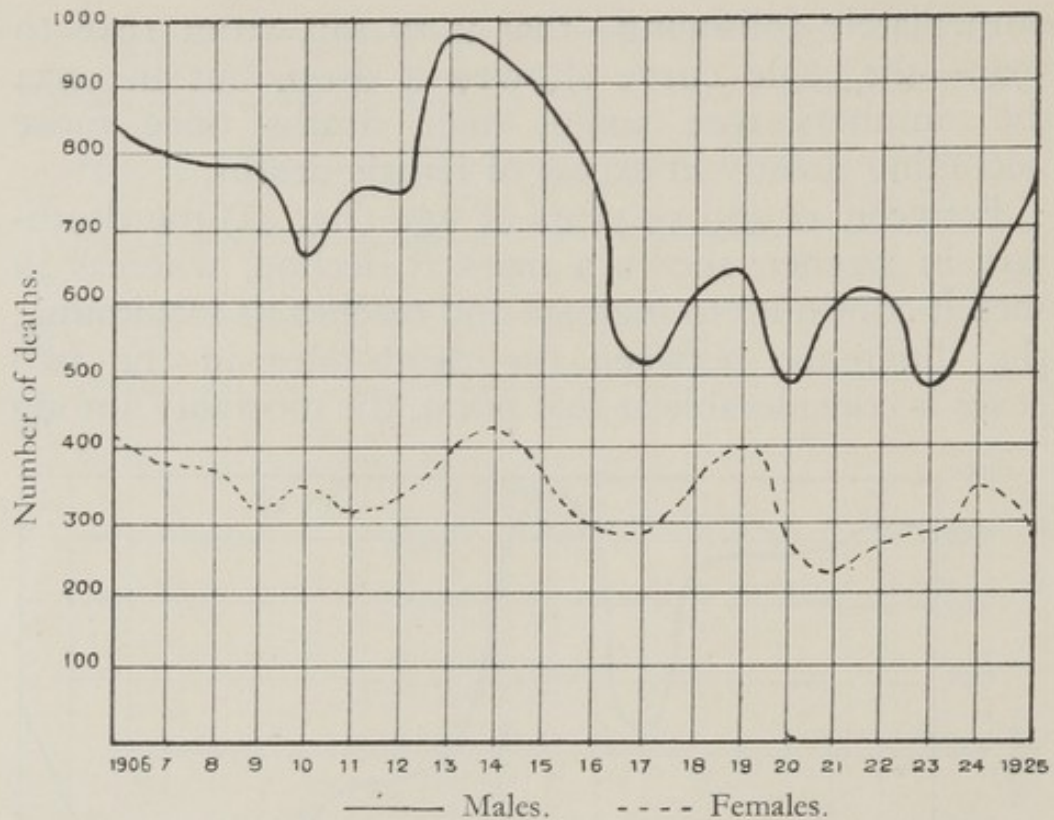


FIG. 42.—Mortality from tuberculosis per 100,000 inhabitants; for the years 1906 to 1925 inclusive. Comparison between the two sexes, from 41 to 50 years of age.

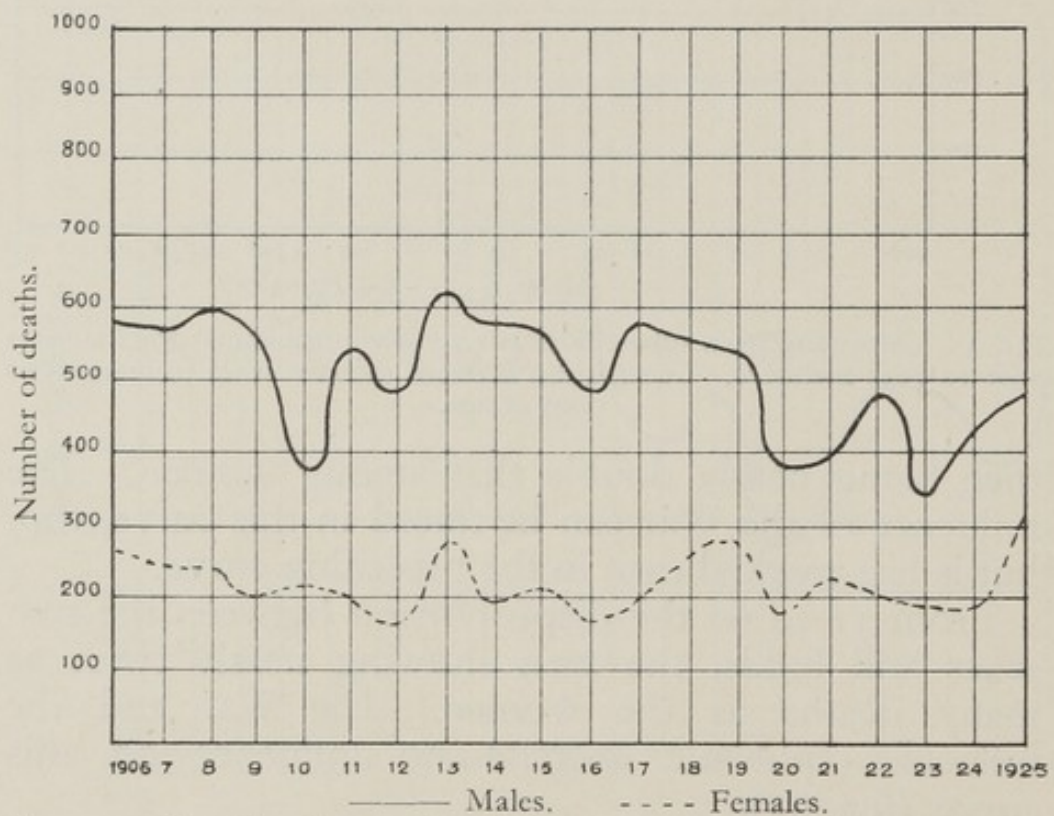


FIG. 43.—Mortality from tuberculosis, per 100,000 inhabitants; for the years 1906 to 1925, inclusive. Comparison between the two sexes, from 51 to 60 years.

each other again, though the death-rate among men is still in excess of the rate in women by about 20 or 25 per cent.

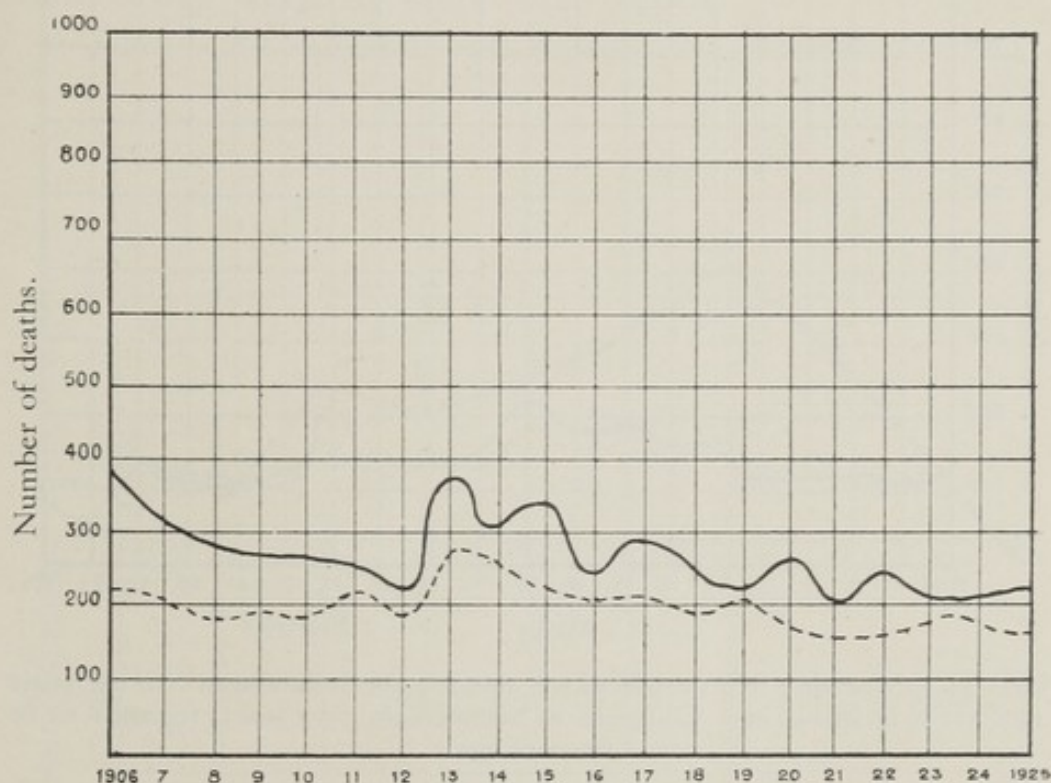


FIG. 44.—Mortality from tuberculosis, per 100,000 inhabitants; for the years 1906 to 1925 inclusive. Comparison between the sexes, from 61 to 70 years of age.

Lastly, in the period between 71 and 80 years of age, the curves in the two sexes again become identical (fig. 45).

Fig. 31 gave a combined picture of these results, and is reproduced here for convenience. It confirms the fact that the death-rate from tuberculosis is substantially the same in men and women up to the age of 25 years, and in extreme old age, as well as showing that during the intermediate period the disease takes heavier toll of men than of women; between the ages of 45 and 55 this difference is so marked, as we have previously noted, that deaths among men are twice as numerous as deaths among women.

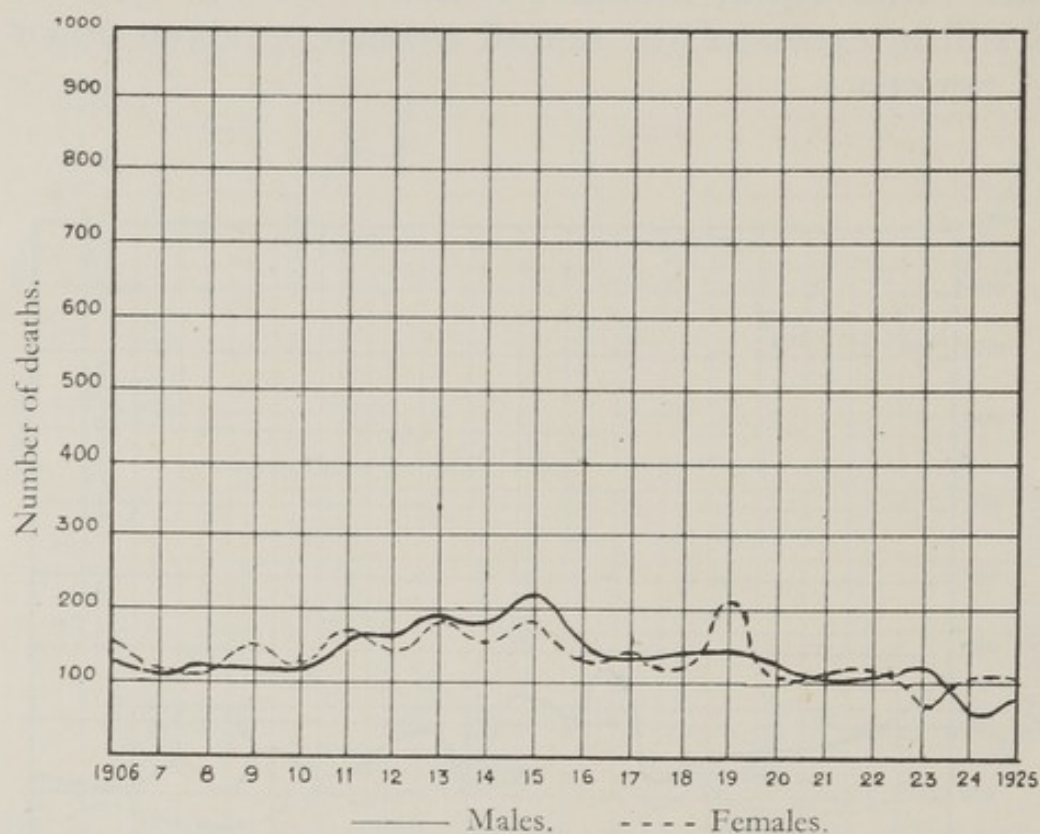


FIG. 45.—Mortality from tuberculosis, per 100,000 inhabitants; for the years 1906 to 1925 inclusive. Comparison between the two sexes, from 71 to 80 years of age.

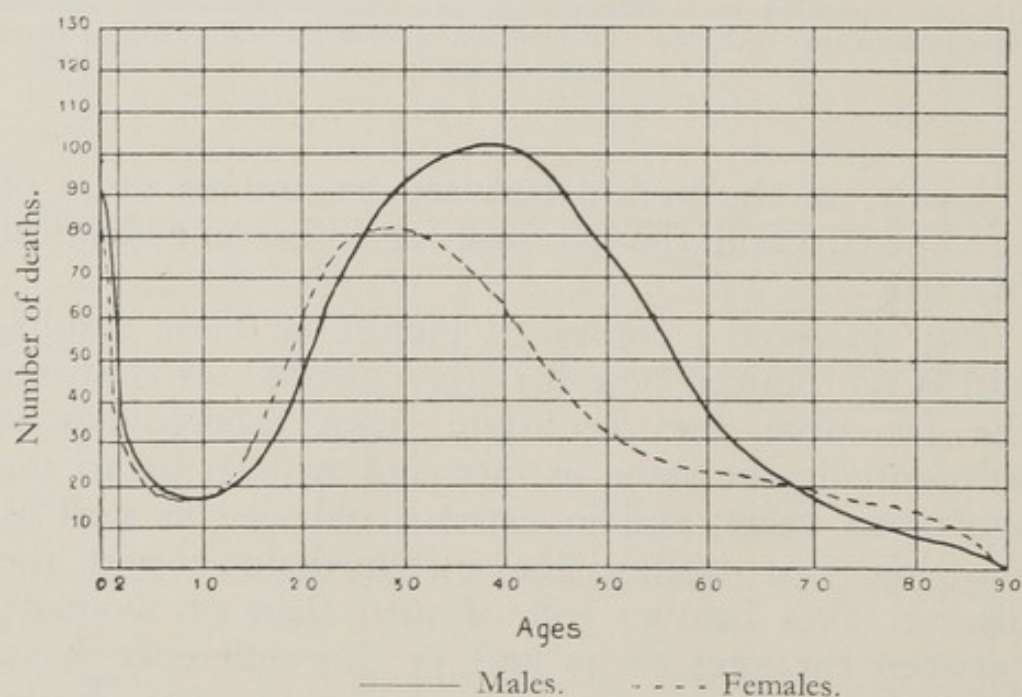


FIG. 31.—Mortality from tuberculosis, per 100,000 inhabitants, calculated according to age and sex, for the years 1906 to 1925 inclusive.

This finding had previously been arrived at in several demographical studies. The statistical department of the *Comité National de Défense contre la Tuberculose* published a similar diagram, which I reproduce below (fig. 46), in their 1926 report.

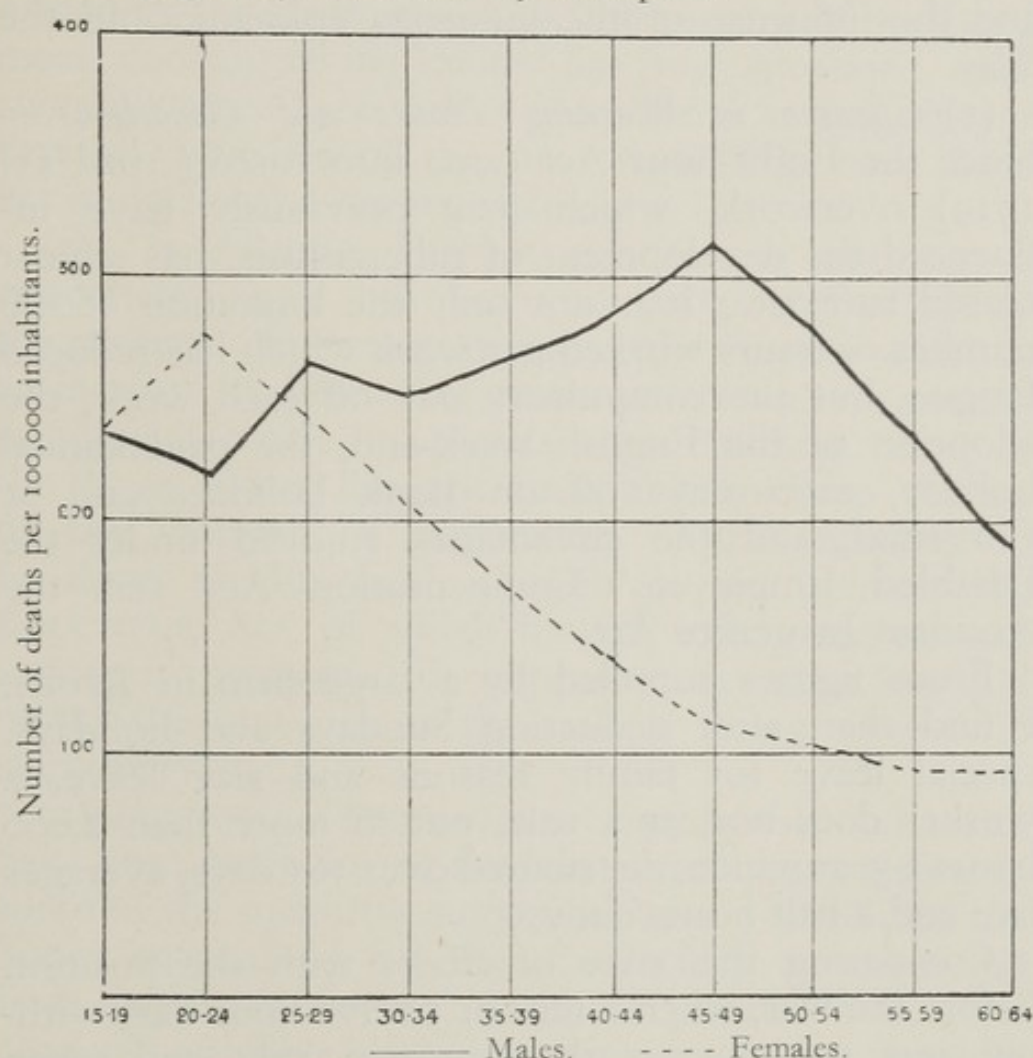


FIG. 46.—Mortality from tuberculosis between the ages of 15 and 65, for the whole of France, for the year 1926. Charted according to age and sex.

C. *Principal Factors exerting an Influence on the Mortality from Tuberculosis.*

The fact emerges from the foregoing discussion that the death-rate from tuberculosis varies more or less considerably according to age, sex and period. The reasons for these variations deserve investigation, but the factors involved are so many that the task is a difficult one. We may, however, consider the principal among these factors with a view to deciding their relative importance, approximately at least.

Among the more noteworthy of these variable factors I shall concern myself especially with the following :—

Working hours and conditions, diet, housing, improved therapeutics and prophylaxis, alcoholism and the influence of the influenza epidemic and the War.

(1) *Changes in Working Hours and Conditions.*—Since the Eight-hour Act came into force (April 23, 1919) overwork, which may previously have influenced the development of tuberculosis, has almost ceased to exist. It is not only the limitation of the number of hours worked per week which has reduced fatigue, but the compulsory day off each week, the adoption of the English week-end, the paid annual holiday, extra days off on Bank holidays and at Christmas, and the advantages enjoyed under the Disabled Employees' Compensation Act and the Accident Insurance Act.

From figures supplied by a large firm in Lyons, I find that, after deducting Sundays and holidays, special leave for family reasons and sick leave, a worker does not, as a rule, put in more than 2,000 hours a year which, distributed over 365 days, averages five and a half hours daily.

Comparing this state of affairs with the position before the war, when a ten- or twelve-hour day, without rest pauses, was the common rule, and when there was no regular off-duty day since at that time Acts for the protection of workers did not exist, or afforded insufficient safeguards—it seems probable that improved conditions of work have contributed to the decline of tuberculosis.

I do not suggest that these legislative measures have been attended with all the advantages which were expected of them, for if they have benefited female workers, they have been a mixed blessing to men ; five and a half hours work a day leaves a good many idle hours, which are too often spent in the public house.

(2) *Changes in Diet.*—There can be no doubt that important modifications have taken place, in the course of the last ten years, in the dietary of the greater part of the population, and more particularly in that of the labouring classes. According to statistics furnished by the abattoir service, the amount of butcher's meat consumed in Lyons has not increased substantially since 1906, but it is notorious and significant that all branches of the provision trade have been booming for the last ten years.

(3) *The Housing Problem.*—As far as housing is concerned, there has been no progress but rather the reverse. For many reasons—the chief of which is an increase in the cost of construction with no corresponding increase in rentals—the building trade in the large towns has not been able to keep abreast of the increase of population. Much remains to be done in this field, though in my opinion the LOUCHEUR Act, of which the full effects are not yet apparent, promises to improve the situation and marks the first step in the task of doing away with slum dwellings.

(4) *Improved Therapeutics.*—Considerable advances have been made during the last twenty years, although some of the measures suggested have not fulfilled the hopes entertained for them. Decided progress has been made, however. Artificial pneumothorax has rendered valuable service in many cases; sanatorium treatment has been extended, and, with the dispensary service, must be regarded as being among our most useful weapons against tuberculosis. The gold salts treatment promises well, but has not yet been given a sufficient trial to permit of its being included at this stage, as an accepted remedy. The same holds true for vaccination with CALMETTE'S B.C.G., which may produce excellent results for the future, but which falls outside the period under consideration. Generally speaking, however, the therapeutics of tuberculosis have shown a decided advance during the last ten years, and must have had an effect on the decline of the disease.

(5) *Prophylactic Measures*.—During the last ten years, war upon the tubercle bacillus has been waged on a larger scale than ever before. An examination of the chart showing the mortality in infants between 3 and 10 years of age (fig. 38) shows that the decrease has been marked since 1920. This indicates, in my opinion, the excellent effects of child welfare services of the GRANCHER type, open-air classes, summer camps, the health-visiting of infants, medical inspection of schools, school dispensaries and so on. In my view, it is to the improved sanitary conditions which are the outcome of these activities that we owe such improvement, rather than to any measures designed to prevent infection.

The results obtained, as a matter of fact, have been more favourable among the children of sound parents for whom there was no fear of infection, than among others. Moreover, the influence of prophylactic measures directed against the bacillus itself is not indicated in any of the documents or statistics relating to tuberculosis.

(6) *Influence of the 1918-1919 Influenza Epidemic*.—The 1918 epidemic had a marked influence on the mortality curve because influenza carried off a number of tuberculous patients whose deaths were ascribed to influenza alone. In spite of this cause of error, the deaths from tuberculosis of girls and young women in 1918 exceeded those for the preceding years, and the premature death of a number of tuberculous women was reflected in a slight reduction in the tuberculosis mortality during the succeeding years.

(7) *Influence of the War*.—To illustrate the effect the War may have had on the general course of the tuberculosis mortality I have charted the death-rate from tuberculosis from 1910 to 1924, so that the War period is shown in relation to the five preceding and the five subsequent years (fig. 47). It shows a decline of tuberculosis during the War period, chiefly among men.

It will be observed that curves for the two sexes run almost parallel during the years preceding the War, the death-rate being higher among men than among women; the curves approach each other between 1915 and 1919 and at the end of the period they almost coincide; after the war they tend to diverge again. It is the decline in the male curve which is responsible for the approximation of the curves, since the death-rate among women during the War period remained almost the same as it was during the preceding five years.

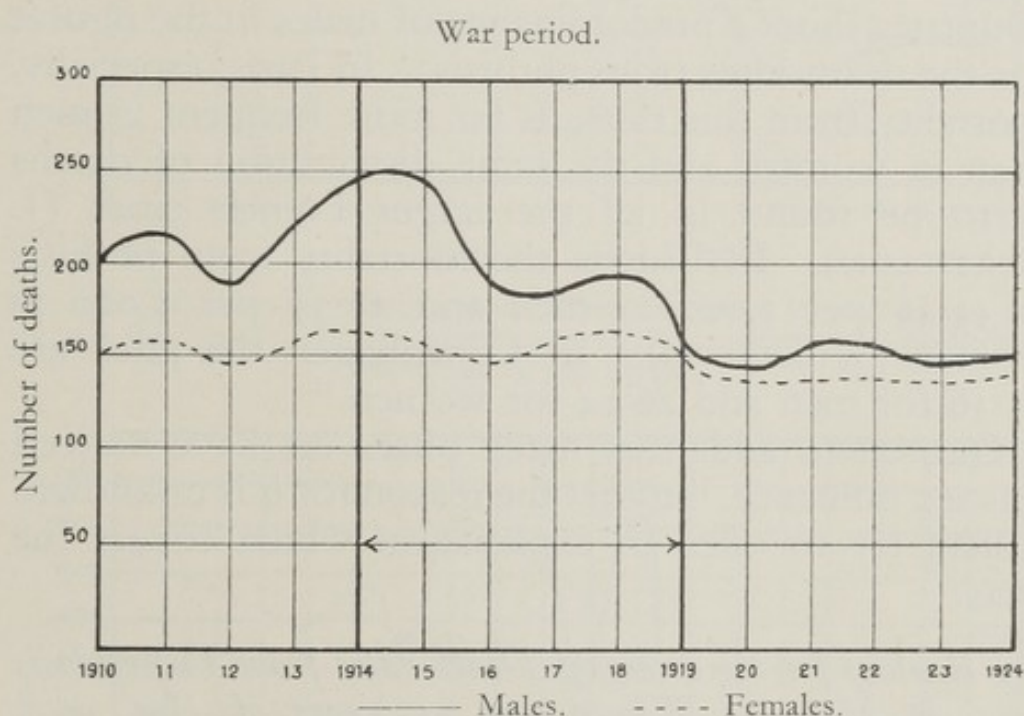


FIG. 47.—Comparison of the mortality from tuberculosis per 100,000 inhabitants, before, during and after the War.

It will be seen that the War had no unfavourable effect on the mortality from tuberculosis, and indeed seems to have produced the opposite result, in spite of the hardships endured by the troops, and the use of asphyxiating gases. Why was this? Doubtless because the influence of alcohol was limited during the war period; the liberal rum and beer rations did not produce the same disastrous effects as aperitifs, or alcohol treated with harmful flavouring agents; probably, moreover, an open-air life helped to dissipate the evil effects of alcohol.

Alcoholism.

Let us inquire into the effects of this important agent in the spread of tuberculosis. Wladimir GRUNBERG, in his 1912 inaugural thesis on *Heredity and Tuberculosis*, pointed out that the disease takes a heavier toll of men than of women: "I have constantly noted in the course of my investigation that pulmonary tuberculosis is commoner in men; among children, far more boys than girls are found to be bronchitic and tuberculous. This influence of sex deserves attention, since statistics for most European countries show a predominance of males in the figures for the death-rates from phthisis. In Paris, especially, mortality from this cause is far more frequent in men than in women, and the same distribution of deaths is to be found in all the larger French cities (J. BERTILLON). In Prussia the mortality from phthisis is 33.48 per 1,000 in men and 28.55 per 1,000 in women (WURZBURG). In Copenhagen the rates are 35.36 for men and 26.14 for women."

GRUNBERG adds that many observers have noticed this sex influence, but that the reason for it is unknown. I shall try to offer an explanation which covers the facts.

D. *Reasons for the divergent Death-rates from Tuberculosis in Men and Women over 25 Years of Age.*

I have taken the sum of the deaths of male and female persons, respectively, which occurred before the thirtieth year of life, during the twenty years under consideration; from these figures I have been able to plot out fig. 48, which shows the close correspondence between the death-rate in the two sexes up to 30 years of age.

In a second diagram (fig. 49) I give the sum of the deaths occurring in persons between the ages of 31 and 70 years of age; this confirms the finding, already noted more than once, that, from the end of adolescence onwards, men provide the bulk of deaths from tuberculosis; when figures showing the total mortality

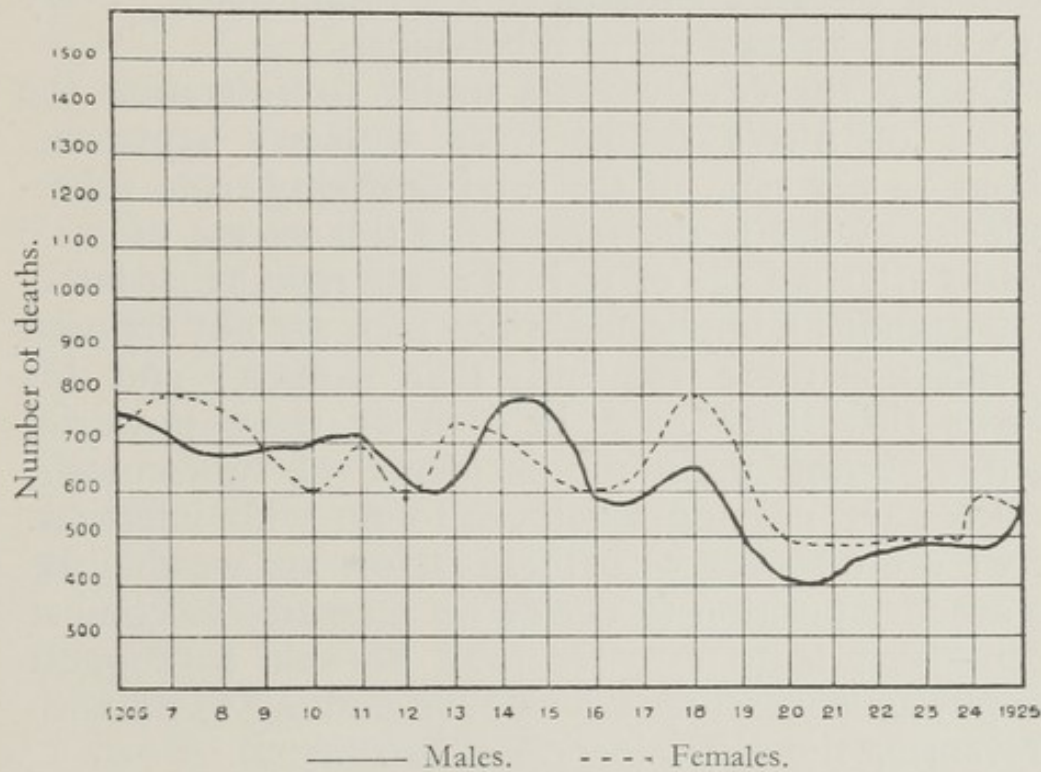


FIG. 48.—Mortality from tuberculosis in persons under 30 years of age, per 100,000 inhabitants, for the years 1906 to 1925 inclusive. Comparison between the two sexes.

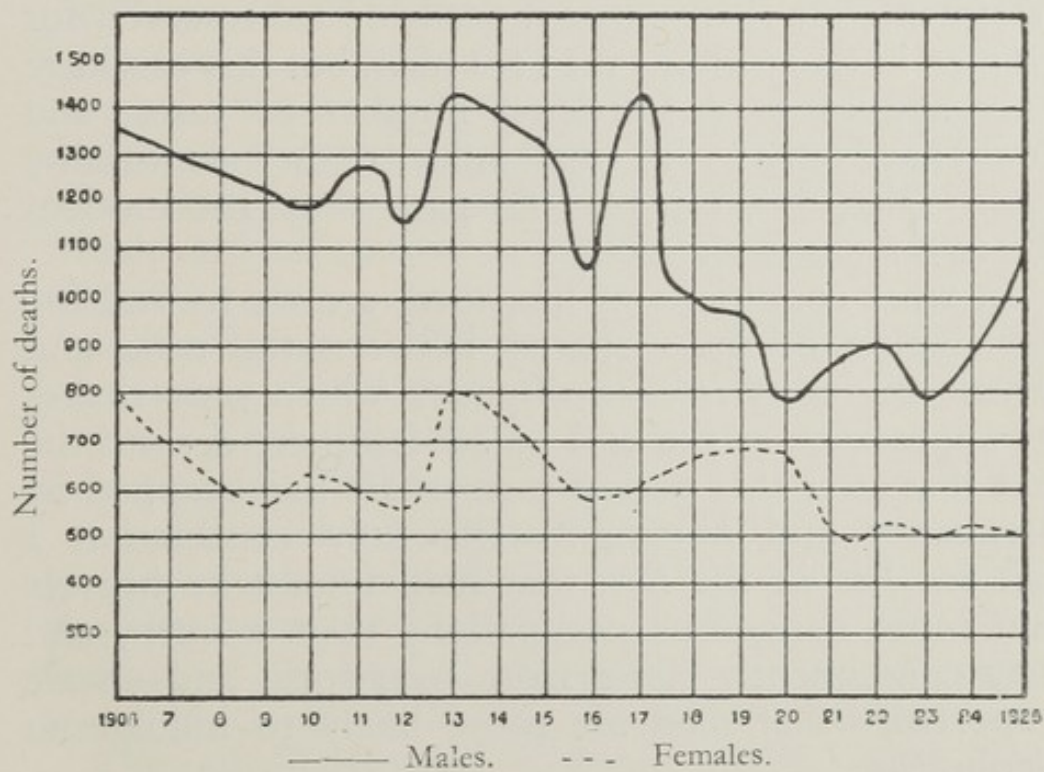


FIG. 49.—Mortality from tuberculosis in persons between the ages of 31 and 70, per 100,000 inhabitants, for the years 1906 to 1925 inclusive. Comparison between the two sexes.

from the disease are examined it is found that for every 15 women 19 men die of tuberculosis.

During the twenty years under consideration the excess of men's deaths over women's represents about 12 per cent. of the total mortality from tuberculosis. What is the reason for this excess of male deaths after the age of 30? Let me repeat that infection cannot be implicated, since men are not exposed to infection more frequently than women; and this shows that there must be one or more powerful factors, acting upon the incidence of tuberculosis, which have nothing whatever to do with infection. If we can discover what these factors are we shall be in a better position to decide on measures to combat them—that is to say, we shall be able to suggest prophylactic measures which have nothing to do with preventing the dissemination of bacilli.

The treatment of tuberculosis is the same in men and women, so we cannot hope to find the explanation of the excessive male mortality in differences of treatment. It is true that more beds are reserved for women in sanatoriums than for men, but this privilege only applies to a restricted number of cases, and could have only a very small influence on the mortality rate. Diet, too, can play no part, since the food of the two sexes is identical.

In what conditions of life, then, are we to find the explanation of the disparity between the male and female mortality rate—a disparity which only makes its appearance at the end of adolescence, despite the fact that after that period women are handicapped by pregnancy and nursing? The only explanation I can see lies in the fact that men undertake heavier and more dangerous occupations than women, and may consequently suffer from overwork, and—more important—that men are more likely to indulge in alcoholism.

As I have shown, overwork scarcely exists nowadays for the majority of workers. A group of women employed in a factory would run a greater risk of being

overworked than their husbands, for while the latter usually go to the public house when the day's work is over, as well as on Sundays and holidays, their wives have to keep the home tidy, cook the food and look after the children.

I do not consider that the more dangerous callings carried on by men have any influence, since the disparity between male and female deaths only appears at the ages of 25 or 30, whereas men may carry on these arduous occupations from the age of 10 or 15. Any influence of the kind should therefore be apparent in the earlier years, and in any case occupations likely to reduce the resistance of the worker are exceptional.

Medical officers of dispensaries have observed that men tend to come later for a first examination than women, and their lesions are often more advanced; I hardly think that this tendency, or the fact that women receive earlier treatment, can be responsible for the marked difference noted. Moreover, if these factors accounted for the higher mortality among men their effects should be apparent between the ages of 20 and 30, as well as later in life; but this is not the case. I cannot, in short, find any explanation of the difference between the male and female death-rate other than bouts of drinking or chronic alcoholism, which are so much commoner among men than women.

It is not easy to decide how much of the mortality rate is due to the first and how much to the second factor. That the part played by alcohol is extremely important, however, will be clear from the following:—

(1) There is a remarkable parallelism between the incidence of tuberculosis and alcoholism; this is evident from the statistics published by the Health Section of the League of Nations, in its 1926 report, from which the following figures are quoted:—

The coefficients of mortality from tuberculosis, per 100,000 inhabitants, were at that time as follows:—

Seville, 40; Sofia, 36; Budapest, 32; Trieste, 31 (cities in which the consumption of alcohol is very high).

Paris, 28 ; Madrid, 25 ; Lille, 25 ; Venice, 24·8 ; Lyons, 24·5 ; Strasbourg, 23 (cities in which alcoholism is beginning to be less widespread).

Barcelona, 16 ; Brussels, 13·5 ; Berlin, 13·5 ; Cologne, 12 ; Hambourg, 12 ; Rotterdam, 11·7 ; Munich, 11·2 (cities in which the consumption of alcohol is notably less than in those previously mentioned).

Lastly, the coefficient drops below 11 in those countries in which prohibition is enforced, namely : Copenhagen, 10·8 ; San Francisco, 10·4 ; Boston, 9·8 ; New York, 9·6 ; Chicago, 9.

LEGRAND, as early as 1906, in his thesis on *Alcoholism and Tuberculosis*, drew the following conclusion :—

(a) That those States in which the consumption of alcohol is greatest have the highest mortality from tuberculosis.

(b) That the death-rate from tuberculosis is especially high in those Departements of France in which alcoholism is widespread.

(c) That the mortality from tuberculosis in large cities is in direct ratio to the number of drinking saloons.

(d) That in any city, the districts which show the highest death-rate from tuberculosis are those in which the sale of alcoholic liquors is greatest.

(2) Fig. 36 shows that in the years immediately following the War the mortality rate among men between the ages of 31 and 70 declined, and approximated more closely to the female curve ; this corresponds to the period during which the *Pouvoirs publics* took steps to suppress the sale of absinthe.

At that time, too, just after the Armistice, a large number of the demobilised troops had lost the habit of frequenting public saloons. The task of resuming civil life or finding new occupations kept many of them away from public houses for a time ; since then, unfortunately, aniseed spirits have replaced absinthe, and their sale is booming, judging by the rise of distillery shares. Men have found their way back to

public bars, the numbers of which may be assumed to be increasing, since there are now 44,000 retailers of wines and spirits in Paris among a total of 90,000 buildings—or about one retailer to every other house. In Lyons there are over 5,000 drinking saloons to 28,000 buildings; and the incidence of tuberculosis among men is again upon the up-grade.

Another interesting fact was reported by MOUISSET in an article which appeared in the *Presse Médicale* of November 19, 1919:—

“The comparatively low percentage of tuberculosis among our prisoners of war, returned from Germany, either before or after the Armistice, was one of the few pleasant surprises of the War. Yet these men, for the most part poorly nourished, had undergone severe mental and physical hardships; during the months or years of their captivity, however, they had been unable to abuse the use of alcohol. May not this enforced temperance have been a beneficial circumstance?”

(3) In the paper by LEGRAND, referred to above, we find the following observation:—

“If, instead of considering the cases of tuberculosis among men as a whole, we divide them up and consider separately those in which alcoholism was a factor, we find that the death-rate among temperate men with tuberculosis corresponds closely with the death-rate among women. It is clear, then, that after a certain age one important factor determines the onset of tuberculosis—namely, alcoholism.”

He also claims that his view is supported by the following table:—

	From 20 to 29 years of age	From 30 to 39 years of age	From 40 to 49 years of age	Over 50
Out of 100 alcoholic subjects how many develop tuberculosis? ..	56	40	37	11
Out of 100 temperate subjects how many develop tuberculosis? ..	36	20	33	5

At all ages, alcoholic subjects are more likely to develop tuberculosis than temperate people.

(4) LESIEUR and LEGRAND have shown experimentally that the consumption of alcohol favours the development of tuberculosis in animals infected with KOCH's bacillus.

(5) Finally, many clinicians have confirmed the fact that *alcoholism prepared the way for tuberculosis*. Among them are LANCEREAU, ARRIVE, COURTOIS-SUFFIT, RACHTS, FRAENZEL, IMBAULT, DE LAVARENNES, BROUARDEL, LANDOUZY, DAREMBERG. MOUISSET and BONNAMOUR, GAUSSEL, LEGRAND, LESURIER, BARBIER and JACQUET, BAUDRAN, HORAND and others.

E. *Arguments against Alcoholism as an Essential Factor.*

The unfavourable action of alcohol has been disputed, particularly by Prof. CALMETTE, who wrote in *La Vie Médicale* : " Since cattle do not take alcohol, it cannot be pretended that alcoholism is a factor in the development of tuberculosis, as far as they are concerned."

I have never suggested anything to the contrary, and it is hard to see what bearing this statement has on the subject under discussion ; we are considering not cattle but the differences observed between the two sexes of the human species.

Prof. CALMETTE, moreover, puts forward some statistics collected by M. ARNOULD, who considers the influence of alcoholism on tuberculosis to be negligible.¹

This opinion clashes with the view of all those clinicians who have specially investigated this problem. M. ARNOULD's interpretation of the figures he quotes in his paper is certainly interesting, but it is in direct opposition to the findings of medical men who have drawn their conclusions from actual cases ; his view, therefore, is not in accordance with the facts.

¹ E. ARNOULD. " Existe-t-il des Concordances Statistiques entre l'Alcoolisme et la Tuberculose." *Revue d'Hygiène*, t. xlvii, p. 614, 1925.

How does he arrive at his conclusions? They are based on purely statistical data, which have been compiled from demographical documents obtained from various sources; different kinds of units have been added together in drawing them up.

His inferences have no sound basis, and do not conform to the principles of scientific logic. Let us consider some of his statements.

"In most countries, more than half the deaths from tuberculosis occur among those members of the community who, *on account of their age*, contain the smallest proportion of alcoholic persons."

This proves nothing about the influence of alcoholism on tuberculosis. Moreover, it was self-evident from the outset, since tuberculosis is responsible for large numbers of deaths among those who are too young to have become alcoholic. To draw from that statement the conclusion that alcohol does not influence the propagation of tuberculosis almost amounts to saying: "The proof that alcohol has no action of any kind is to be found in the fact that infants of less than a year in age, who have never drunk any alcohol, may die from tuberculosis."

M. ARNOULD has simply overlooked the fact that there are other and more important factors than alcoholism which influence tuberculosis, and determine the age distribution of the cases.

It is an accepted rule, though one too easily forgotten, that where a problem involves several variable factors, no conclusions can be legitimately drawn if only one variable is taken into consideration. M. ARNOULD has neglected all the variable factors except one, and his conclusions are therefore valueless.

According to the same observer: "The disparity between the two sexes in regard to the incidence of alcoholism, between the ages of 30 and 60, though it varies in different countries, is always considerable; while the disparity in the incidence of tuberculosis between these ages is similar in different countries, and, moreover, is fairly small."

On the contrary, the disparity between the two sexes in regard to the incidence of tuberculosis between the ages of 30 and 60 is not always small. It is sometimes marked, notably round the age of 40. In Lyons, in the course of 20 years, tuberculosis was responsible for twice as many male deaths as female deaths at that age. This emerged from the statistics I collected with the help of Dr. VIGNE, to compile which we reviewed and classified 188,000 death certificates.

In addition, the marked disparity between the mortality-rates in the two sexes at the age of 45 shown in my own figures corresponds exactly to that shown in the curves published by the statistical service of the National Defence against Tuberculosis Committee (*see* fig. 46, p. 187).

Jacques BERTILLON, between 1901 and 1906, also drew attention to the difference in the mortality rate between the two sexes. I reproduce the curve which he published at the time (fig. 50) showing that in Paris this difference in persons over the age of 25 was even more marked than it was in Lyons.

M. ARNOULD questions the harmful action of alcohol by using the following argument :—

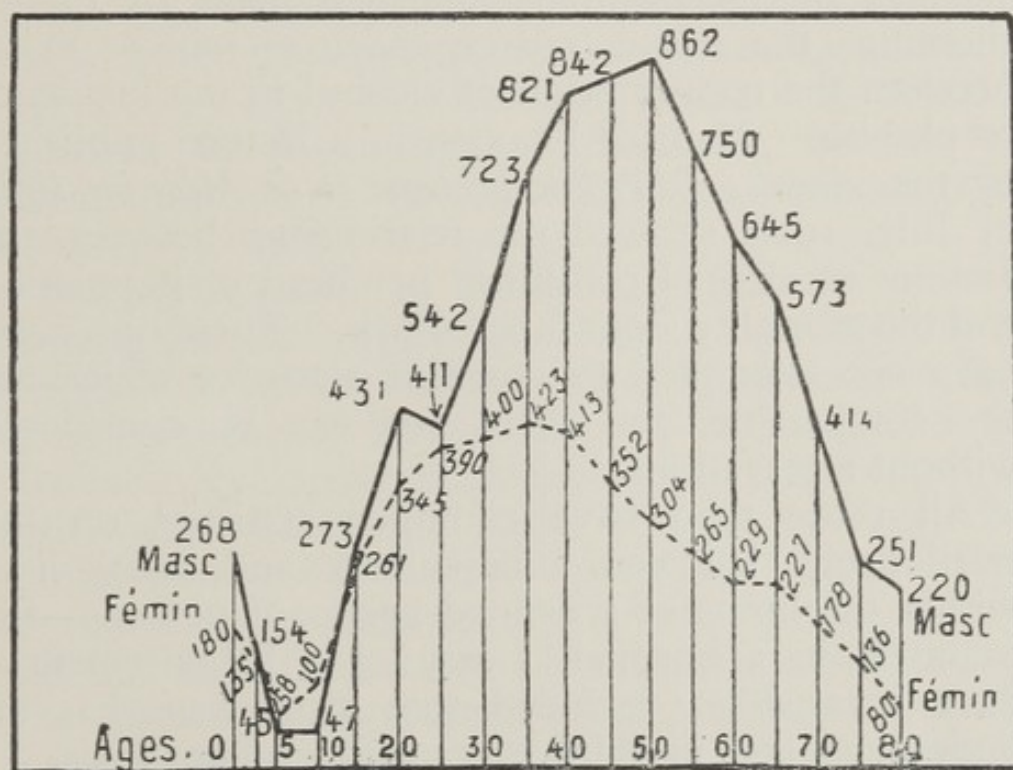
“According to statistics covering some thirty years, the consumption of alcohol per head of population has not decreased in England and Germany in the period reviewed, while the death-rate from tuberculosis has declined to half its former figure.”

This does not prove that alcohol has nothing to do with the incidence of tuberculosis, for there are many factors influencing the mortality rate from the disease, some of which tend to lower it. Even if we assume that the influence of alcohol has remained unchanged, there is nothing to prove that these other factors exert no effect in producing the decline in tuberculosis.

Incidentally, the statement that the consumption of alcohol has remained constant in Germany does not appear to be borne out by information from other sources; possibly M. ARNOULD's information is out of date.

His ultimate conclusion is cautious. "There is no correspondence," he says, "between the incidence of tuberculosis and the incidence of alcoholism, so far as the figures available show."

This is perfectly true, but it does not prove that the influence of alcoholism on tuberculosis is non-existent ; moreover, M. ARNOULD is unwise to stigmatise the findings of clinicians, who have had direct access



Paris : Out of 100,000 inhabitants of each sex, and at different ages, how many succumb to tuberculosis in one year ?
(1901-1906.)

The dotted line represents the female mortality, the continuous line the male mortality. The vertical lines indicate 10-year periods. The numbers represent the annual average for the years 1901-1906 in Paris.

FIG. 50.—Difference between the mortality rate in the two sexes, at various ages. Paris, 1901.

to cases, as hypothetical, and to accept as a basis for argument a series of statistics drawn from various sources and compiled on varying principles ; it is not possible to compare such figures without making careful reservations. The inferences drawn from such data are themselves hypothetical and, in my view, misleading. By taking statistics from other sources, opposite conclusions could be reached.

Several observers have found, when examining controlled and comparable statistics, that "the places in which the mortality from tuberculosis is highest are those in which the consumption of alcohol is greatest" (LANDOUZY and BROUARDEL). The same observers hold that "out of 100 consumptives seen in hospital, 71 will be found to be alcoholics.

A statistician, whose competence will not be denied, Jacques BERTILLON, has published maps of France showing the close correspondence which exists between the consumption of alcohol in the incidence of phthisis. Maurice PERRIN, in a lecture published by the *Annales d'Hygiène publique et de Médecine légale* of July, 1916, showed the relationship between the amount of alcohol consumed per head of population and the mortality from tuberculosis. These observers have not attempted to combine statistics which are not comparable, and their data can be considered without reservations.

All those who have compiled statistics on the relationship between tuberculosis and alcoholism within the limits of a defined group of persons—for example, in a hospital, a city or a Département—have invariably concluded that alcoholism has an undoubted and harmful effect upon tuberculosis.

Why is M. ARNOULD the sole exception? Because he argued from a hotchpotch of statistics which could not properly be compared with each other, and based his inferences upon these irreconcilable data.

The opinion of clinicians who have been brought face to face with facts and not statistics is unanimously opposed to the view that alcoholism has no influence on tuberculosis.

"The greatest danger of alcoholism is tuberculosis" (LANCEREAU).

"To attempt to combat the tuberculous toxin without combating the alcoholic toxin is like trying to prop up an old wall which is crumbling at its foundations" (LEGRAIN).

"Attempts to control tuberculosis will be unsuccess-

ful if they do not strike at the root of the evil—alcoholism.”

“Alcohol fosters phthisis.”

“Above all, let us attack alcoholism. Alcoholism favours the development of phthisis in three-quarters of the cases which occur among the working class in Paris” (RENDU).

At the Tuberculosis Congress held during October, 1905, the influence of alcoholism on tuberculosis was admitted by ACHARD and GAILLARD, LANCEREAU, CHEYSSON, COSTE, A. ESPINAY Y CAPO of Madrid, GRENIER DE CARDENAL of Bordeaux, GAUTRY of Clermont-Ferrand, MERCIER of Tours, TRIBOULET of Paris, and COSTE.

But let us return to the facts. LEGRAND showed that dogs, animals which are relatively unsusceptible to tuberculosis, will withstand the intravenous injection of an emulsion of KOCH's bacilli; alcoholised dogs, however, develop tuberculosis. LEGRAND in common with other observers, states that in animals, the administration of alcohol fosters the development of tuberculosis, hastens the course of the disease, and increases the chance of pulmonary localisation. The disease is aggravated by alcoholism, especially if the drink of choice is absinthe. After an inquiry covering several thousand hospital cases, LEGRAND arrived at the conclusion already quoted above, namely:—

“If, instead of considering the cases of tuberculosis among men as a whole, we divide them up, and consider separately those in which alcoholism was a factor, we find that the death-rate among temperate men with tuberculosis corresponds closely with the death-rate among women. It is clear, then, that after a certain age, one important factor determines the onset of tuberculosis—namely, alcoholism.”

GAUSSEL, in comparing the tuberculous and non-tuberculous cases in GRASSET's wards in hospital, found the following proportions of alcoholics: in a series of 100 tuberculous cases there were 69 alcoholics,

and in a series of 100 non-tuberculous cases there were 58 alcoholics. The incidence of tuberculosis, therefore, is higher among persons addicted to alcohol than among temperate or teetotal persons.

Jules COURMONT, in Lyons, reached analogous conclusions in 1910. Among 1,000 cases admitted to his wards he found 442 alcoholics and 558 moderate drinkers; among the 442 alcoholics, 200 (45 per cent.) were tuberculous and 75 died in hospital, whereas among the 558 temperate patients there were only 41 cases (7.34 per cent.) of tuberculosis.

From whichever side the problem is approached, the noxious influence of alcohol upon tuberculosis is evident. I know of no clinician or laboratory worker who has found evidence to the contrary. Let me recall once more the curious observation made by MOUISSET, who examined the prisoners of war returning from Germany; he expected to find a high proportion of tuberculous cases among them, in view of the privations they had endured, in some instances for several years, but to his astonishment they were free from tuberculosis. During their period of captivity they had had no access to alcohol.

In my own diagrams, illustrating the mortality rate in men and women between the ages of 30 and 70, it was shown that the disparity between the death-rates in men and women decreased just after the war, and I was able to correlate this closer approximation of the curves with certain consequences of the War itself, and with the suppression of absinthe. The influence of these two factors has been disputed on the ground that men between the ages of 30 and 50 were away at the Front; this criticism is inaccurate, however, for it was immediately after the campaign—from 1919 to 1922—that the death-rates in the two sexes approached more closely to each other, and by that time all the men between 30 and 50 had returned home.

In view of the observations discussed in this chapter, I am convinced that alcohol has an important influence upon the incidence of tuberculosis and that

a vigorous attack on alcoholism would be a far more effective method of prophylaxis than any measures designed to prevent the dissemination of tubercle bacilli.

I cannot help wondering how the opponents of this view explain the fact that after the age of 35 twice as many men die from tuberculosis as women, and that according to LEGRAND's observations the excess male deaths occur entirely among alcoholics.

A friend of mine, a medical practitioner in Strasbourg, has drawn my attention to the objectionable effects of tobacco, and to the repercussion of chronic nicotine poisoning on the incidence of tuberculosis. He is inclined to take the view that smoking is almost more harmful than drinking as a factor in the production of tuberculosis. I do not think that this can be the case, for inquiries conducted in hospital, which give such significant evidence in regard to alcoholism, do not reveal a similar correspondence between tuberculosis and over-indulgence in tobacco-smoking. Nor does the disparity between the male and female mortality-curves appear to be less marked in countries where the use of tobacco is restricted than in those where smoking is prevalent. Be this as it may, the constant irritation caused by smoking and the toxic effects of nicotine possibly influence the onset or progress of the disease, and it might be expedient to inquire more closely into this new problem.

F. *Conclusions.*

Alcoholism undoubtedly paves the way for tuberculosis, and the disease will attack the drunkard, whatever his environment. Whether that environment is infected or not, tuberculosis will develop in the terrain prepared by alcohol, much as rot invades old trees, and the affected subject becomes a new source of the disease which, only too often, he passes on to his children.

The alcoholic persons who become tuberculous represent only a small proportion of those who suffer

from alcoholic poisoning. Many of them resist tuberculosis or may develop hepatic or mental conditions.

There must be some other factor then, apart from alcohol itself, which influences the development of tuberculosis in the drunkard. The bacillus itself comes into action, and we may wonder whether its presence is determined by direct infection, or by the sudden lighting up either of a hereditary condition, or of an infection acquired soon after birth. In view of the fact that an alcoholic subject will develop tuberculosis even when not in contact with a tuberculous environment, I do not consider it likely that infection can be implicated here, any more than it can elsewhere; it seems more probable that there is a lighting-up of infection in a terrain which has been rendered favourable by alcoholic poisoning. In this way alcoholism extends the age limits within which latent tuberculosis commonly shows itself.

An investigation into the heredity of such cases, and into the chances of postnatal infection, would throw some light on this important question. Such an investigation should not be conducted in the casual way adopted in making similar inquiries in the past, in consequence of which no reliable data have been obtained; it should include only those cases in which a thorough investigation of the family history has been possible.

It is more than likely that the incidence of tuberculosis would decrease rapidly if it was not constantly augmented by the steady stream of cases which owe their origin to alcoholism. Every year more of these cases appear, and counterbalance the effects of public health measures and therapeutics alike.

In view of our inability at the present time to cure tuberculosis, *an attack on alcoholism, in my opinion, offers the best hope of reducing the evil, and is the most hopeful method of prophylaxis among adults.*

If I have failed to convince the reader, let me ask him to find a plausible explanation of the following

fact, which has been thoroughly established by my statistics and diagrams :—

Over a period of 20 years in Lyons (and elsewhere in France, no doubt), tuberculosis has caused the deaths of a considerably larger number of men than of women, but only in persons between the ages of 30 and 70.

CHAPTER X.

TERRAIN HEREDITY.

TERRAIN heredity may be the outcome of two distinct factors : it may result from the transmission of certain properties of the body fluids which favour the growth of the bacillus ; or it may possibly be the outcome of organic changes brought about in the infant, either by the transmission of secondary and impermanent cell characteristics which were present in the tuberculous parent, or by defects in nutrition due to alterations in the mother's body fluids. In this chapter I hope to investigate the inheritance of the properties of body fluids, on the one hand, and the inheritance of organic characteristics on the other.

A. Inheritance of the Properties of Body Fluids.

Despite the barrier offered by the placenta to the free communication of fœtal and maternal blood, it is none the less certain that the fœtus is impregnated with substances which circulate in the mother's vessels. The impermeability of the placenta is relative, since the nourishment of the fœtus has to pass this obstacle ; not only the large protein molecules succeed in penetrating it, but certain parasites which are considerably larger.

In order to establish the occurrence of terrain heredity on a scientific basis, attempts have been made for some years to find, in the fœtal blood, the same toxins or antitoxin properties which are present in the blood of the mother. Positive results were first obtained by REYMANN, working with goats ; he found that in every case the antitryptic, antistaphy-

lolytic, antivibriolytic and agglutinant properties of the mother's blood were transmitted to her kids. He found that in the early weeks of life the blood of the kids showed these specific properties in a marked degree, and in some cases they were secondarily augmented about a month after birth ; this secondary elevation he ascribed to properties acquired from the maternal milk.

According to the experiments of ROSENAU, THEOBALD-SMITH and ANDERSON, young guinea-pigs, born of animals which have been sensitised with horse-serum, retain the anaphylactic condition transmitted by their mothers for several weeks ; moreover, NATHAN-LARRIER and RICHARD found that mixed serums, injected into the mother during pregnancy are not arrested by the placenta but pass into the blood-stream of the fœtus, though in amounts too small to cause sensitisation. In only a few cases did sufficient antigen pass the placenta to confer active sensitisation on the fœtus, beginning during uterine life, and reaching a maximum from two to three weeks after birth. According to these observers, such anaphylaxis is not inherited from the mother, but results from the fœtal reaction to the antigen ; which alone is capable of passing through the placenta.

HOWEL, EBY, WEGELIUS, KREIDL and MANDL, and MERKEL confirmed REYMANN's findings in other animals, and observed that the hæmolytic, precipitating and agglutinating properties transmitted to the fœtal blood gradually decreased, and finally disappeared between the third and sixth week of life. So that the body fluids of the young did not retain these inherited properties.

The same facts have been observed by ACHARD in the human species, in connection with the agglutinating reactions of the blood towards EBERTH's bacillus ; MARX has noted the same phenomenon with SCHICK's reaction which, when negative, denotes the presence of diphtheria antitoxin in the serum. Statistics

show that 93 per cent. of new-born infants have a negative SCHICK reaction, and that the proportion of positive reactions has increased to 56 per cent. by the end of six months, and to 91 per cent. by the end of a year.

DEBRE and JOANNON found that an infant born of a mother who has had measles is completely immune to the disease during the first two months of life, but gradually becomes susceptible to it, so that at the end of six months the child retains no trace of his former immunity. Analogous findings have been recorded in regard to the properties acquired by the body fluids as a result of tuberculosis; the transmission of the agglutinating properties of the serum and the complement fixation reaction are the two phenomena which have been the subject of special inquiry in this field.

CHAMBRELENT and BUARD, ANDERODIAS and BUARD, F. ARLOING, ROMBERG, DECOS and LAGRIFOUL have thrown some light on the first point, by showing that it is possible for the agglutinating properties of the blood to be transmitted from a tuberculous mother to her child, but that it only occurs in exceptional cases and to a small extent.

The transmission of the BORDET-GENGOU reaction is much commoner. First observed by PARISOT and HANNS, the transmission of this reaction was confirmed, in CALMETTE's laboratories, by Esther ROSENKRANTZ, who found evidence of it in 31 per cent. of cases; later, as we have already seen, it was confirmed afresh by RIBADEAU-DUMAS, CUEL and PRIEUR, and finally by COOKES in America.

MARCEL LELONG¹, in 1925, repeated and confirmed these observations, and reached the following conclusions :—

“(1) Transmission of tuberculous antibodies from the mother to the fœtus through the placenta is an ascertained fact, and occurs frequently.

¹ Marcel LELONG. “L'Enfant issu de Parents tuberculeux.” *Thèse de Paris*, 1925. Imprimerie de l'Aisne, Laon.

“(2) This transmission is not merely a question of filtration ; the placenta is not a passive organ. It arrests certain antibodies, and concentrates others so that a higher proportion of them enters the foetal circulation than that found in the maternal blood ; by this process of concentration the placenta may even cause antibodies to appear in the foetal blood which cannot be detected in the maternal circulation. Its duties vary, therefore, according to circumstances, and it may be called upon to arrest, concentrate or reactivate different antibodies as occasion arises.

“(3) The tuberculous antibodies transmitted by the mother to the foetus do not remain long in the blood of the new-born child ; their concentration decreases rapidly during the first eight or ten weeks, and by the end of the third month they have nearly always disappeared completely.

“(4) The disappearance of these maternal antibodies is an automatic phenomenon, connected neither with a transmitted tuberculous infection nor with the presence of a tuberculin reaction ; nor is it influenced by the development of an acquired tuberculous infection. It occurs whether the infant is well or ailing, likely to live or likely to die.

“(5) In the infant an acquired tuberculous infection does not stimulate the production of tuberculous antibodies ; it is only rarely, and late in the disease, that the infant is capable of manufacturing antibodies.”

Marcel LELONG comments on these conclusions as follows :—

“To sum up, the transmission of tuberculous antibodies from mother to foetus shows clearly that ‘something’ passes the placenta, but a closer investigation shows that this ‘something’ rapidly and invariably disappears. From the point of view of tuberculous heredity this fact is awkward to interpret, for the significance of these antibodies is unknown. I cannot think they have any influence on the fate of the child, since they disappear equally rapidly in those who do well and in those who do badly.

“An inquiry into the fate of infants segregated from their parents at birth will show whether this opinion is correct. For the moment, we can simply state that the transmission of antibodies from mother to child proves that, at birth, the infant is still in the state of a parasite upon the maternal tissues, and only assumes its individual biological state a few weeks later.”

These conclusions appear to me to be rational. In actual fact all the specific properties of the serum—agglutinating, antitoxic, antihæmolytic and so on—are only anaphylactic phenomena caused by the invasion of foreign proteins; if these properties were transmitted as permanent characteristics from parents to children, the immunity present at birth would persist indefinitely, and this is disproved by observation. If these properties were not lost they would steadily accumulate; as a new property was acquired it would be transmitted to the offspring, and added to the pre-existing properties, with the result that the body fluids would show an increasing instability. Not all the functions of the body fluids, however, depend upon anaphylaxis, and it is conceivable that properties of another order might be inherited by the offspring.

Heredity is a highly complex phenomenon, as yet mysterious and perplexing. The following example is peculiar as being a case in which the cells rather than the body fluids retained the parental imprint. I observed this case in person, and it aroused my curiosity to a considerable extent.

In my own family there was a female relative, long since dead, who had a habit spasm which might only appear at intervals of days or weeks; it generally escaped the notice of strangers, and only members of the family had observed it. It consisted of a rapid gesture in which she took hold of her nose between the thumb and forefinger of her right hand; her remaining fingers, at first extended and joined, were laid upon the left cheek and then, by a rotary

movement, were made to sweep across the lips; the fingers would bend and the hand would finally close as it was drawn away from the face. She was the mother of six children, none of whom inherited this trick; one of her daughters had two girls, who were also free from it, and the elder of these had in her turn one daughter and two sons. What was our astonishment to see the same tic appear, and recur with annoying frequency, in the younger boy when he was about three years of age. This child had never seen his great-grandmother, and had seen none of his relations perform the characteristic gesture, which had been forgotten long before by everyone in the family.

Through what mechanism could this phenomenon have been reproduced? What was the nature of the profoundly latent impulse which was transmitted with extraordinary accuracy through three generations, without modification and yet without affecting the intermediate subjects?

Does it correspond to a temporary modification of certain groups of cells, or to some interference with their nutrition by the body fluids? Permanence of the species does not come into question here; it is only the transmission of impermanent and secondary characteristics which is under discussion.

In the face of such an example one begins to wonder whether liability to infection might not depend to some extent upon unknown modifications of the cells or body fluids, transmitted by some unsuspected process. We are not in a position, however, to do more than theorise, since we are entirely ignorant on this point; we can deny nothing and prove nothing.

B. The Inheritance of Organic Characteristics by the Children of Tuberculous Parents.

The question which now arises is to decide whether the newly-born children of tuberculous parents present non-bacillary lesions, or whether they have certain organic characteristics which predispose them to the development of tuberculosis.

It is recognised that the children of tuberculous patients often show definite physical peculiarities which have been described by ROBIN, CHARPY, VOILLEZ, FREUND, HIRTZ, LANDOUZY, DELPEUCH, DARIER, GIOVANI, VIOLA, FICI and others. These physical peculiarities are as follows :—

Dolichocephaly, oval face, long and slender neck, elongated thorax flattened antero-posteriorly, long and narrow lungs, sloping shoulders, downward and forward inclination of the upper and lower thoracic openings, narrowing of the xiphoid angle, retracted hypochondria, vertical sternum, broad and abruptly sloping intercostal spaces, aplasia of the first costal cartilage, strongly-marked inclination upwards and inwards of the upper costal cartilages, reduced lateral surface of the thorax, slight exaggeration of the normal cervico-dorsal kyphosis with prominence of the seventh cervical vertebra, raised diaphragm, small heart with an almost vertical longitudinal axis ; a slender and small-boned skeleton, the legs long in comparison with the arms, a minimum of soft tissues with a maximum surface area, exaggerated reflexes, small viscera, organic inefficiency, little muscular strength, deficient adipose tissue, hyperactivity of the sympatheticotonic hormones (thyroid, suprarenal, pituitary) and of the chromaffin system, and in some cases renal insufficiency, hyperplasia of the lymphatic system, auburn colour of the hair, hypertrichosis, softness and fineness of the features and intelligence above the average.

This characteristic picture, however, is never complete ; some of the qualities described will be present while others will be absent, or scarcely marked ; some of them, indeed, are not confined to tuberculosis but may be encountered in other pathological or even physiological conditions. It is true, none the less, that they are found with impressive frequency among consumptives, and they cannot be ignored in discussing tuberculous heredity.

Unquestionably subjects presenting these physical

peculiarities are more prone to tuberculosis than normal persons, and the question of organic terrain heredity would be settled as far as this point is concerned if there was not a serious argument against it.

These predisposing physical characteristics, supporters of the theory of infection assert, are real enough, but they are acquired, not congenital. The infant is normal at birth, he is infected by his parents after birth, and the toxins of the bacillus alter nutrition so profoundly as to produce the physical peculiarities observed. On this assumption, the characteristics of the tuberculous patient would be consequent on an infection acquired in early infancy, and would not be a factor predisposing to the development of tuberculosis.

Let us try to decide how much this objection is worth.

In the first place, we may note that disturbances of metabolism caused by microbic toxins undoubtedly produce certain degenerative effects, which are shown in changes in the skin and hair, in BARTEL's hypoplastic state, PALTAUF's thymo-lymphatic conditions, BRISSAUD's infantilism of the Lorain type, dwarfism, gigantism, and delayed sexual development.

Such degenerative syndromes are clearly different from structural deformities. The morphological changes which we are discussing have been demonstrated in three different ways: by experiments on animals, by post-mortem examinations of infants who die within a short time of birth, and by clinical observations.

Before reviewing the evidence obtained in these three ways, a question naturally presents itself: in tuberculous patients the genital cells are unavoidably exposed to the influence of the bacillary toxins; is it possible that this influence causes the ovum to develop along pathological lines?

The functions of the primitive male cell, like those of the female cell, may also be influenced by the toxins of the bacillus; if the mother is tuberculous the product of conception is liable to be

influenced still further by the toxins which pass through the placenta. We cannot as yet decide the part played by each of these processes in influencing foetal growth.

Let us consider the attempts which have been made to elucidate this problem.

(1) *Experiments on Animals*. — CHARRIN inoculated tuberculosis into a female guinea-pig at the beginning of pregnancy; twenty-three days later, five young were born, two of which succumbed immediately and a third died the same night; the remaining two died at the end of the first week; he reports that all of them showed signs of hepatic degeneration.

These hepatic changes have been investigated by NATTAN-LARRIER¹ and DELAMARRE; they consist of congestion which may be associated with interstitial hæmorrhage, mild cirrhosis, and parenchymatous degeneration.

In young guinea-pigs, born of a tuberculous mother, a marked hæmatopoietic reaction is present at the time of birth; the liver, in fact, is not the only organ affected, congestive lesions being present in the spleen, kidneys, myocardium, thryoid and suprarenals.

In a series of 54 rabbits conceived by tuberculous mothers 25 died before birth (MAFFUCCI, BAUMGARTEN, GARTNER). The conditions under which such experiments are conducted, however, are quite different from those which obtain with human subjects. Experimental inoculation of a rabbit or guinea-pig is not comparable with human tuberculosis; massive subcutaneous injection of bacilli has nothing in common with ordinary conditions of infection. The duration and course of the disease, and the period of pregnancy are totally different in animals and human subjects, and the anatomical and placental peculiarities, as well as the organic characteristics, differ according to species; so that it is difficult to draw any rational inferences from the foregoing experiments.

¹ NATTAN-LARRIER. "Les Premiers Stades de l'Hérédité Pathologique. Recherches Histologiques." *Thèse de Paris*, 1901.

The heavy death-rate among the young of female animals experimentally inoculated with tuberculosis undoubtedly indicates, however, the harmful influence of the bacillary toxin on fœtal development.

(2) *Lesions discovered at Post-mortem Examination of Infants born of Tuberculous Parentage.*—These lesions have also been studied by CHARRIN and NATTAN-LARRIER, and later by P. RIVIERE who, in his 1902 thesis, summarised his post-mortem observations on the visceral lesions in the infants of tuberculous patients¹.

“In those infants of tuberculous mothers who die shortly after birth (though labour may have been normal, and the child may have experienced no serious illness during its brief existence), post-mortem examination will reveal, in a certain number of cases, profound changes in some of the viscera which, however, do not present any of the characteristics of the maternal disease.

“The numbers of infants showing these signs vary according to the conditions, and the nature and extent of the tissue changes are also variable.

“An exception must be made, however, in respect of the liver, the secreting cells of which always show degenerative changes, while the other elements of the parenchyma also show modifications; but these changes are not identical in all subjects.

“These organic modifications date from the intra-uterine period. When the short life (undisturbed by any serious infection or intoxication) of the infant is taken into account, the extent, intensity and nature of the lesions make it evident that they must have existed before birth

“The variability of the lesions, and their non-specific nature, can easily be explained, in spite of their identical origin. It is now recognised that a single organism may be responsible for diverse actions; some observers have succeeded in extracting from

¹ Paul RIVIÈRE. “Des Lésions non-bacillaires des Nouveau-nés issus de Mères tuberculeuses.” *Thèse de Paris*, 1902.

KOCH's bacillus various principles—sclerosing, hæmorrhagic and so on. It is possible that the secretions of the bacillus influence the fœtal tissues, and owing to the diversity of their properties these toxins alone may be responsible for the various anatomical and pathological changes observed.

“Furthermore, to the tuberculous toxins may be added the toxins of organisms secondarily infecting the tuberculous lesions in the mother, and the toxins derived from the defective functioning of injured organs. These secondary infections, as well as the state of auto-intoxication, are complications of the primary disease ; so that we may legitimately blame the primary disease for the effects of these secondary products on the fœtus. Let me add that the influence of the maternal condition makes itself felt to a variable extent : survival for a more or less prolonged period is compatible with certain mild degenerative lesions ; thanks to the data obtained we can make some guess at the origin of the various lesions which may appear.”

Investigations along the same lines were made by Marcel LELONG, who examined histologically the organs of 14 infants, born of tuberculous parents, and either stillborn or separated from their parents at birth. In 10 of them he could find no lesion worthy of the name in the organs examined : no congestion, leucocytic infiltration, sclerosis or parenchymatous degeneration. In the remaining four obvious but variable lesions were found in the liver, ranging from slight congestion to fatty degeneration, which LELONG ascribes to gastro-intestinal troubles which had been observed in these infants during life. According to this observer, the information obtained from the post-mortem examination of four still-born infants was far more instructive, since in these cases it was possible to eliminate the chief source of error, namely, the influence of extra-uterine life in the external environment. The infants in this series, apart from one, all showed perfectly normal structure ; the exception was born of a syphilitic mother and died

five minutes after birth ; on examination this child showed periportal sclerosis and a somewhat marked hæmatopoietic reaction, with enlarged liver and spleen.

LELONG concludes : " That in the viscera, and especially the liver, of infants born of tuberculous parentage, no lesions are to be found which can be regarded as being indirectly traceable to a maternal intoxication."

Faced with such an inconsistent statement I am nonplussed. Among the infants examined by RIVIERE, several died within a few hours of birth, when the influence of the external environment could not have had time to make itself felt, and there are no grounds for denying the existence of tissue changes in these cases. Moreover, it is possible that the three fœtuses which LELONG describes as showing no changes may have been born of mothers in whom the tuberculous lesions were not elaborating markedly toxic products. We cannot, therefore, draw any definite conclusions from these three cases, and further investigations would be necessary to establish his view ; in the meantime, I can honestly say that I should think it remarkable if the impregnation of the fœtus, for months on end, with the products of tuberculous activity, produced no organic changes.

The high incidence, among the children of tuberculous parents, of congenital debility and marasmus—which may cause the death of the infant long before a tuberculous infection acquired after birth could have developed sufficiently to prove fatal—seems to indicate that the influence of the tuberculous toxins is not so innocuous as LELONG's conclusions might lead one to suppose.

(3) *Clinical Observations.*—The physical characteristics associated with tuberculosis are undoubtedly found in the children of parents who, affected only with closed local lesions, could not have infected their children, since they are not disseminating tubercle bacilli either in their sputum or in any other

of their secretions. The same characteristics will be found in children whose tuberculous fathers died before their birth, and who have been carefully kept out of reach of infection.

Demonstrable cases of this kind are all too few at the moment, because too little attention has been paid to the collection of reliable data along these lines ; records of the kind should be checked by means of careful and exact statistics.

The organic deformities which are often seen in tuberculous patients are frequently seen in their children as well, although the children may be free from the disease. *It can scarcely be argued that the physical characteristics which they present is the result of an infection so trifling that it is impossible to detect the slightest sign of it.*

These numerous objections lead me to conclude that an organic hereditary predisposition towards tuberculosis, in the offspring of tuberculous parents, cannot be denied.

It seems remarkable to me to pretend that the infants of tuberculous mothers are normal and free from the disease at birth, when clinicians and laboratory workers agree that abortion and premature delivery frequently occur in women or animals suffering from acute tuberculosis, and that the offspring born of such parents are frequently feeble and under-developed.

In a series of 143 fœtuses born of tuberculous mothers, 30 were stillborn, and 24 died prematurely (DE RIENZI, LANDOUZY and LÆDERICH). Some suggestive statistics collected by COUVELAIRE show that in a series of 357 fœtuses or newly-born infants, the offspring of tuberculous parents, 10·6 per cent. were registered as stillborn, or deceased within three days of birth, and 14·4 per cent. succumbed within the first month of life.

MANGLIAGULLI, of the Institute of Obstetrics at Milan, found that out of a series of 229 pregnant tuberculous women, miscarriage before the sixth

month occurred in 15, and premature delivery between the sixth and eighth month in 93; the number of stillbirths was 42.

Similar findings led ROGER to state that in tuberculous patients "the fœtus does not develop normally, and premature labour is frequent."

MONCKEBERG expressed the same idea when he wrote: "I can assert that all the infants I have seen born of mothers seriously affected with tuberculosis have died, most of them during the first few months of life; while those who were born of mothers in whom the tuberculous condition was less serious, developed poorly, made progress only with difficulty, and readily succumbed."

In view of these facts can it be maintained that heredity is of no importance in tuberculosis?

C. Non-specific Terrain Factors.

So far we have considered the influence of the terrain only from the point of view of heredity; non-specific properties of the body fluids, however, seem to have a considerable influence in determining the onset of the disease, as several authorities have shown, including BEZANÇON, and SERGENT and his pupils.

Owing to the fact that the theory of infection is still accepted by most medical practitioners, it has been suggested that changes in the body fluids, favouring the development of tuberculosis, do occur, and that the terrain is thereby rendered suitable for infection.

I consider that I have shown that tuberculosis is not infectious, or is scarcely infectious, to adults, and in my view the influence of changes in the body fluids upon the development of tuberculosis is through quite a different process. I am convinced that, in subjects who are affected hereditarily, a potential source of the disease is present in the form of the organism itself, which may remain latent for years, but which abandons its saprophytic state and becomes active

as soon as the conditions of its environment become favourable to growth.

Although this question falls outside the subject of my argument—which is to discuss the parts played by infection and heredity in the ætiology of tuberculosis—it will not be out of place, I think, to remind readers that other factors play a part in the development of the disease.

I will content myself, however, with summarising the discussion, and will refer readers who wish to study the subject more fully to the masterly paper by SERGENT and TURPIN¹ on this subject.

One of the principal arguments urged in support of the “terrain” factor is that the various animal species do not react in the same way to tuberculous infection. The guinea-pig, which is extremely susceptible, develops a lymphatic form of tuberculosis, while cattle tend to develop generalised tuberculosis with frequent pulmonary localisations comparable to those found in the human subject. In swine the digestive tract is chiefly affected and in dogs the disease attacks the viscera. The horse is less susceptible, and the goat and sheep are resistant to the infection.

It should be noted that these differences in susceptibility are not entirely the outcome of varying properties in the body fluids, but are also dependent upon variations in cellular function and organic characteristics which vary in different species.

The fact that certain therapeutic agents influence the course of the disease in one way or another seems to indicate that the properties of the body fluids are not negligible, quite apart from any question of specificity. It is possible, moreover, that the course of the disease, depending on whether it is attacking an infant or an adult person, is influenced by properties of the body fluids which vary with the age of the subject.

¹ SERGENT and R. TURPIN. “Les Facteurs de Terrain, autres que l’Allergie, dans l’Infection tuberculeuse.” *Révue de la Tuberculose*, t. viii, No. 2, April, 1927, pp. 200-221.

Changes in the body fluids due to fluctuation in the secretions of the endocrine glands—for example, at puberty, the menopause and during pregnancy—may also exert an influence on the tubercle bacillus; the same holds good for over-activity of the endocrine system.

Lastly infections, intoxications, chills, defective diet and unhealthy living conditions may play a part in preparing the terrain for the growth of the tubercle bacillus.

Alcohol, however, the agent which does most to modify the tissues and the body fluids, has not been given sufficient attention so far. I cannot insist too much on the principle that prophylactic measures should be chiefly directed against this factor, which is far more powerful in its effects than sanitary, climatic or dietetic factors; as far as adults are concerned an attack on alcohol offers the only hope of efficient social action against the tuberculosis peril.

CHAPTER XI.

THE INFLUENCE OF THE THEORY OF HEREDITARY TUBERCULOSIS ON SOCIAL PROBLEMS.

IN view of the difficulty of disproving the influence of heredity upon tuberculosis, some observers have tried to show that the acceptance of this idea would involve serious consequences, and would be detrimental to the social system. Some of my opponents, insufficiently informed of my arguments, have managed to grasp a sort of parody of them, in which every detail is exaggerated. My views with regard to infection in adults are taken as applying generally, and are mistakenly extended to include infants. Arguing on these lines they would have been quite logical if they had charged me with discouraging public interest in the child welfare societies, particularly those which are the outcome of GRANCHER'S admirable work, to the detriment of such institutions ; this charge, however, is quite unfounded and is due to a mistaken conception of my views.

I have never held that tuberculosis is not infectious to infants, but have always admitted the contrary, and have tried to account in a rational manner for such infection ; so that I approve fully the principle of early segregation of infants from their tuberculous parents.

To bring my argument into disrepute by accusing me of hindering the work of the child welfare societies, and to misrepresent my statements to such an extent as to make them convey the exact opposite of their original meaning, would be a most unjust proceeding did it not spring from a regrettable lack of information. If it sprang from malice it would be libel, and I should meet it with stern measures.

Some of my opponents, no doubt at a loss for any reasonable objection which they could offer to my views, had recourse to innuendo and tried to arouse against me the hostility of the ex-service men whose lungs had suffered in the War; they made it appear that if tuberculosis was admitted to be hereditary, the men who developed tuberculosis during the War could not be regarded as having acquired the disease as a result of war service, and would lose their pension rights.

Such opponents forget, or pretend to forget, that I regard heredity as only one factor in the ætiology of the disease, an important factor, it is true, but one which can be resisted if the system is not debilitated, but is fit to defend itself against the attacks of the latent bacillus in the body. The hardships of war undoubtedly helped to transform the bacillus in its innocuous form into a pathogenic agent, and reduced the resistance of those who had to endure them, so that the development was favoured of lesions which otherwise might never have revealed themselves.

The unhappy victims of consumption acquired as a result of war service have nothing to fear from a bogey which has been conjured up by desperate controversialists.

Finally, I have excited a passionate protest among philanthropists interested in institutions which set out to combat tuberculosis, by suggesting that infection may not occur between adults and that the disease may be hereditary after all. Such a doctrine cannot be accepted, they declare, since it implies that all the work which has been done to prevent dissemination of the tubercle bacillus is futile. Too much progress has been made along the lines advocated in the textbooks for them to be abandoned now. How could we admit, they ask, that so much propaganda, so much publicity in the Press, so many leaflets and posters and so much expense has been wasted, or almost wasted? How could we confess that in advocating the painful separation of consump-

tives from their families, in treating them as dangerous to their fellows, we have unjustly deprived them of the care and attention which would have been bestowed on them by their relatives ?

I agree that such admissions would be painful, but ought truth to be subordinated to personal convenience or to the interests of certain societies and organisations, however much they may be respected ?

Truth is advancing. Its progress cannot be arrested, and the acknowledgment of an error in directing the fight against tuberculosis will only be more painful the longer it is postponed and the more numerous the obstacles placed in the way of a return to the proper course.

From the practical point of view, has my argument suggested any profound modification of the existing methods of controlling tuberculosis ? Have I said, for example, that a consumptive has more chance—or as much chance—of cure in the confined air of a cramped tenement than in a sanatorium ?

Questions Raised by the Accepted Theory.

After replying to the objections brought against my view, I am forced to recognise that the arguments which I have put forward against the accepted theory remain unanswered. Discrepancies between fact and theory remain unexplained if the influence of heredity is denied, and infection is regarded as the sole means of spreading the disease.

In rounding off this work I will take the liberty of reminding my opponents of the lines they will have to follow, and the questions which they must answer, if they wish to attack the theory of heredity.

I think, however, that I have built on firm foundations, and that the pickaxe which is to undermine them has not yet been forged.

(1) To demonstrate the occurrence of infection in adults, cases of conjugal infection would have to be found, in which the existence of hereditary infection was excluded by thorough clinical and radiological

examination of the parents of the patient. I am still waiting to hear of a single example of this kind; a large number of examples would be necessary, however, to establish the occurrence of conjugal infection.

(2) Examples of infection among persons constantly in contact with tuberculous patients would have to be obtained: that is to say, cases of infection among specialists in tuberculosis, male and female nurses, and nuns giving nursing service in hospitals. As before, the presence of tuberculosis in the parents of the patient would have to be rigidly excluded. Here, too, I am waiting to learn of a single example of infection; and a sufficiently telling number would have to be produced before it would be justifiable to conclude that infection occurs among adults. If an adequate number of cases cannot be found it must be admitted that infection is almost non-existent among adults.

(3) Conversely, some explanation should be given of the fact that the cases are legion in which conjugal infection and infection in the course of professional duties do *not* occur.

(4) In addition it would be necessary to prove that, in a country where the death-rate from tuberculosis represented one-fifth of the total mortality rate, the incidence of conjugal tuberculosis causing the deaths of both partners, was in excess of 4 per cent., and the incidence of tuberculosis causing the death of one partner was in excess of 11 per cent. of the total number. These statistics would have to be strictly compiled and controlled.

The following questions also require answering:—

(5) If tuberculosis is not hereditary, why should tuberculosis, or signs of old tuberculosis, be found almost invariably in the parents of patients, provided the examination is properly carried out?

(6) How is it possible to explain the fact that the child of a tuberculous father, who died before the child's birth, usually dies of tuberculosis whatever preventive measures are adopted?

(7) If a woman has several children by a healthy husband and one by a tuberculous lover, why should the child of the lover be the only one to develop tuberculosis, though the other children brought up in the same environment, remain sound, and the mother herself is unaffected?

(8) How is it that patients suffering from closed tuberculous lesions (such as POTT's disease, coxalgia, arthritis or tuberculous synovitis), and in whom fistula formation has not occurred, so that they cannot disseminate tubercle bacilli, frequently give birth to children who, despite the utmost precautions against infection, ultimately develop tuberculosis?

(9) Why is it that the normal, acid-fast bacillus—which is the form of the bacillus disseminated by consumptives, and is therefore the only one which can be implicated as an infecting agent—when administered to animals, fails to produce in them the delayed, chronic, regressive and often curable type of the disease found in man? This failure, moreover, occurs whatever the species, breed, age or sex of the animals and whatever the dosage and the method used to introduce the organisms into the system.

(10) How is it, on the other hand, that the human type of the disease can be reproduced in the same animals by infecting the embryo, or by inoculating it with the filtrable virus or the saprophytic form of the bacillus?

(11) How can allergy, as the term has been understood so far, be accepted both as a sign of predisposition to the disease and of immunity? Why does it possess two contrary properties?

(12) In the children of tuberculous patients, if it is assumed that the characteristic physical appearance is not congenital, how is it possible to explain the fact that such characteristics may exist in persons whose parents could not have infected them because the parental lesions were closed and therefore incapable of disseminating bacilli? The typical physical characteristics could not be produced, in such cases, by the disease or its toxins after birth.

(13) How can repeated reinfections be regarded as dangerous when the mortality of infants exposed to infection decreases the longer they remain in contact with their tuberculous parents?

(14) Again, if reinfections are dangerous, why do the husbands or wives of tuberculous patients, the medical attendants and staffs of sanatoriums, escape the disease?

(15) In view of the fact that the filtrable virus is transmitted *in utero* to 90 per cent. of the infants of tuberculous mothers, and that the acid-fast bacillus itself passes through the placenta in three cases out of four, as well as the toxic products of bacillary activity, why should it be supposed that the fœtus remains unaffected by them?

(16) How can the curve of allergy be made to correspond in any way with the mortality curve? They appear to be irreconcilable.

(17) Why should the mortality from tuberculosis be comparatively heavy during the first year of life, and then show a rapid decline, as though the onset of infection had occurred before birth?

Tuberculosis does not cause rapid death immediately after infection, nor does infection necessarily occur immediately after birth. If a postnatal infection was the deciding factor, the mortality should be negligible during the first few weeks, or even during the first few months of life, and should then increase steadily for a year or two. Why is this not the case?

(18) Why should allergy, a protective reaction in infancy, disappear at the end of adolescence and reappear after the twenty-fifth year in women and the thirty-fifth year in men, yet remain unchanged in the husbands or wives of tuberculous patients and in the medical and nursing staffs of sanatoriums?

Why have no answers been put forward to all these riddles? In my opinion the reason is simple.

No answer can be found so long as attempts are made to explain matters on the accepted theory; the task is an impossible one, and this shows that the theory must be wrong.

The absence of any satisfactory reply and the failure on the part of my opponents to substantiate their objections confirms me in my belief that I am on the right track.

CONCLUSIONS.

Having answered the arguments put forward against the first edition of this book, I will now consider any modifications which I may have made in my original opinion.

Without prejudice, and without giving undue weight to my own findings, I must honestly confess that, as a result of the foregoing discussion, my belief in the theory of heredity and in the non-occurrence of infection between adults has been strengthened; and that far from shaking my opinion, the objections made to it have only convinced me the more thoroughly of its soundness.

I do not hesitate to admit, however, that my opinion on certain minor points has varied considerably. The necessity for finding fresh arguments, and for examining my previous statements with a more exact scrutiny has led me to revise my views on certain points and to complete certain details of my theory which my previous investigations had not covered.

Of course the view which I have set out is, and always will be, provisional. I believe it to be far closer to the truth than the accepted theory, but none the less I regard it as temporary and susceptible of modification as our knowledge extends.

Let me put it as follows :—

KOCH's acid-fast bacillus, the form of the bacillus found in the sputum of consumptives, and the only form which comes into the picture as far as post-natal infection or inoculation is concerned, never causes, in man, a continuously progressive type of the disease, without remissions, and with uniform symptomatology ending in death. This form of the bacillus, however, is used in all kinds of animal experiments to produce disease of the VILLEMINS type; it is also the form of the bacillus implicated

in the infection of the infant shortly after birth, and generally leads to death from meningitis in the first or second year of life.

But when inoculated into animals, or when it infects a human subject at any age from the time of his birth upwards, this form of KOCH's bacillus never causes the usual type of human disease so frequently described already—the type which kills the vast majority of consumptives, the type which, after years of latency, may choose one of many sites to manifest itself: pulmonary, pleural, osseous, synovial, articular, cutaneous, glandular or visceral; the type, moreover, which is often protracted, usually shows remissions, and which even at times heals completely, especially if the lesion is one of those classified as “surgical tuberculosis.”

This human, clinical type of tuberculosis, chronic, protean and curable, can only be reproduced in one of two ways: either by infecting embryo, or by inoculating it with filtrable virus. This explains why the delayed type of human tuberculosis is hereditary: it can only proceed from infection of the fœtus.

Starting from this idea, which is supported by all the experimental work on tuberculosis, the phenomena of the disease at once become explicable. Discrepancies disappear, and confusion vanishes. The 18 queries set out above, which are unanswerable according to the accepted theory, are resolved at once by the theory of heredity.

(1) Since the acid-fast bacillus is unable to cause infection in man under ordinary conditions of life, or able to cause it only in rare cases, conjugal infection will be found to be almost non-existent, if the facts are properly observed.

(2) The same is true of adult subjects living in a tuberculous environment.

(3) Conversely, the many cases in which conjugal infection and infection in the course of professional duties fails to occur at once become explicable.

(4) As a corollary, it is obvious why the death-rate among married couples, in which both partners succumb to tuberculosis, does not exceed 4 per cent., this being the figure established as probable by the laws of chance, if infection is assumed to play no part in the matter.

(5) If the occurrence of hereditary tuberculosis is accepted, the discovery of signs of tuberculosis in the parents of affected persons (and such signs will always be found if properly sought) is explained.

(6) The theory of heredity also explains why the child of a tuberculous father who died before the child was born, may become tuberculous in spite of every precaution being taken to safeguard him against postnatal infection.

(7) The same theory accounts for the fact that the child of a tuberculous lover may become tuberculous while the remaining children in the family, coming of a healthy father, remain sound, although they may all be brought up in the same environment.

(8) Nor, once the theory of heredity is accepted, is there anything mysterious in the fact that patients with closed tuberculosis (such as Pott's disease, cox-algia, arthritis and tuberculous synovitis, without fistula formation), who have never disseminated tubercle bacilli, may give birth to children who become tuberculous in spite of strict measures to avoid infection.

(9) The characteristic property of the acid-fast bacillus—a property which biologists have failed to appreciate, and which makes it impossible for the organism to cause, after birth, the chronic, protean, regressive and curable form of tuberculosis—explains why infection of the infant during the postnatal period leads to a rapidly progressing and fatal type of the disease.

(10) The human type of the disease can be produced fairly easily in animals by infection of the embryo with the acid-fast bacillus; hereditary transmission is therefore the explanation of the ordinary type of the human disease in its delayed form.

(11) The tuberculin reaction, being merely anaphylactic, is an indication of relative immunity not only in hereditarily affected persons, or in infants affected shortly after birth, but also in persons who, born of parents who were free from the disease, have succeeded in destroying those tubercle bacilli which have attacked but failed to infect them, and who have consequently acquired the vaccinal anaphylactic state.

This reaction is independent of the disease. Since the two may co-exist, however, it is easy to understand why confusion has arisen; as a result of this confusion the tuberculin reaction has been regarded sometimes as a predisposing factor, and at other times, when it exists in the absence of any signs of tuberculosis, as indicating a condition of resistance. This explains the confusion which has arisen about allergy, which attributes to it both predisposing and immunising properties.

(12) The theory of heredity explains the characteristic physical appearance found in the children of parents with closed tuberculous lesions. Neither bacilli, nor toxins, in such cases, could be responsible for infection after birth, or cause the characteristic physical development. The influence must have been exercised congenitally.

(13 and 14) It is by confusing the anaphylactic reaction of the body fluids (to tuberculin derived from the proteins of the bacillus) with the disease itself that observers have come to lay emphasis on the dangers of reinfection, dangers which the facts show to be non-existent. The death-rate from tuberculosis among infants decreases the longer they remain in contact with their tuberculous parents. Moreover, reinfection appears to be negligible in the cases of wives and husbands of tuberculous patients and of the medical and nursing staff at sanatoriums.

Children born of parents who are free from tuberculosis achieve the anaphylactic state through trans-

mission of some property which does not cause infection but confers immunity; whereas children born of tuberculous parents are congenitally affected with the disease and will later develop the common delayed type of tuberculosis, progressing by means of a series of alternating exacerbations and remissions. These exacerbations are wrongly ascribed to re-infection; as a rule, they occur when there has been no opportunity for fresh infection.

(15) It is clear that the filtrable virus must be responsible for delayed and mild types of tuberculosis, since it was by using the tubercle virus in this form that observers such as PAISSEAU and OUMANSKY were able to produce, in animals, that variety of the disease which is never obtainable with the acid-fast bacillus.

The argument, put forward by the supporters of the theory of heredity to bolster up their view, that the filtrable virus derived from the maternal blood-stream has no effect on the fœtus, is inconsistent with experimental findings.

(16, 17 and 18) There is no reason why the curve showing the mortality at different ages and the allergy curve should coincide, since they illustrate two distinct phenomena. The allergy curve indicates the increasing frequency with which an anaphylactic condition is found as age advances, such anaphylaxis being conferred by the entrance of specific proteins into the system and not by infection; the longer the subject remains in a tuberculous environment—that is to say the older he grows—the more frequent will be the opportunities for such proteins to enter the system.

The curve showing the mortality rate, however, depends upon more complex factors, notably on two distinct types of the disease, the importance of which varies at different ages. In early infancy tuberculosis is due to the acid-fast bacillus, which may have reached the patient in one of two ways: either by congenital transmission, so that it is present in the body at

birth, or by postnatal infection during the first few weeks of life. Tuberculosis acquired in either of these ways is usually fatal within the first two years of life, and this explains why the mortality curve shows a peak shortly after birth and declines rapidly from the third year onwards. The second type of the disease begins to influence the death-rate during and towards the end of adolescence; the latent period is explained by the time required for the filtrable virus or the saprophytic organisms, which have been present in the body since before birth, to develop into the pathogenic form of the bacillus. It is hereditary tuberculosis which is responsible for the ascending curve up to the age of 25 in women and 35 in men.

Many persons with hereditary tuberculosis resist their prenatal infection, and succeed in overcoming it by destroying the organisms before they become pathogenic. Certain factors, notably alcoholism, interfere with the body's power of resisting and destroying the infection, and thus extend the period during which the organism may undergo pathogenic development.

* * * * *

My theory, consistent in all respects with the facts, is opposed to the conventional dogma which has been accepted by the medical profession for many years. The theory of heredity indicates the futility of prophylactic measures which begin and end with an attempt to prevent dissemination of tubercle bacilli; (such measures, however, are applicable where infants are concerned, since infants alone are liable to be infected by the acid-fast bacillus).

I realise that those who have devoted themselves to extending prophylaxis along these lines must be reluctant to admit that their efforts have been wasted. I recognise, too, that those observers who have formally declared themselves to be convinced of the theory of infection may hesitate to go over to the opposite point of view and admit they have been on

the wrong track. Hence they will adopt any trick to overthrow my views and bolster up their own prestige.

This is in accordance with human nature, and I entertain no delusions about the immediate fate of my theory and the investigations which support it. They will be rejected just as, in the past, the theory of the earth's motion or the bacterial theory of infectious disease were rejected. GALILÉE, PASTEUR and other pioneers of knowledge would have been less meritorious if they had not had to defend their discoveries against fixed ideas and prejudices. And I, however modestly, shall follow the example of these illustrious predecessors, because I am convinced that I am approaching the truth. I shall defend my views with perseverance but without obstinacy, and shall always be prepared to make the *amende honorable* if there is occasion; but I shall not be ready to do so until arguments are placed before me which are less flimsy and more logical than those advanced so far. Nor shall I ever be inclined to recant in favour of the accepted theory, with its confusions and flagrant inconsistencies which would scarcely be accepted by a blind man.

* * * * *

Following this discussion I shall probably be asked—and quite rightly—“Now that you have finished your destructive criticism what constructive suggestions have you to offer?”

If attempts to prevent the dissemination of the bacillus are futile, how are we to conduct our campaign against this disease? I am chiefly concerned with the cause of the disease, in the hope of being able to strike at the root of the difficulty. But what are the causes of tuberculosis? Let me outline them once more:—

(1) The infant at birth may already have in his body the acid-fast bacillus, which will kill him within the first few days, weeks or months of life.

According to the statistics which I have been able

to collect, cases falling into this class only comprise 0.5 per cent. of the total number of deaths from tuberculosis. This figure is so low as to be almost negligible, and in any case we are powerless against the disease when it has this ætiology.

(2) Acid-fast bacilli, disseminated by a tuberculous parent, may infect the infant soon after birth. The disease progresses without remissions to a fatal termination, usually from meningitis, within the first year or two of life.

Against tuberculosis caused in this way we may usefully direct the prophylactic measures already advocated—namely, segregation of the infant from its parents and its removal to an environment in which it will be protected against all chance of infection.

I will say nothing at this time about the method of vaccination, as we are not yet in a position to consider it.

If methods of segregation, and precaution against infection, were strictly enforced and were always successful, how much might we hope from them? Deaths from tuberculosis among those infected after birth include most of those cases which end fatally between the ages of 3 months and 4 years, and do not, according to my figures, represent more than 8 per cent. of the total number of deaths from tuberculosis. Segregation, therefore, would not save, at the outside, more than 10 per cent. of the total number of those we wish to protect.

(3) By far the most important cause of tuberculosis is that which is responsible for 90 per cent. of cases, including all the delayed, regressive and curable varieties of the disease, and which I consider to be of congenital origin.

It is here that we need some new plan of campaign if we are to get better results.

I can see no heroic means of achieving this purpose, since measures comparable to those applied to leprosy, the one disease which is strikingly analogous to

tuberculosis, are not to be contemplated. Complete segregation of patients in leper colonies has prevented the congenital transmission of leprosy among persons of healthy stock ; but the same principle cannot be applied to tuberculosis. The tuberculosis colonies required would have to open their doors to too large a fraction of the population.

Must we abandon the fight ? I do not believe so. Transmission of the disease to offspring is not unavoidable. Organic reactions tend to destroy the transmitted organisms, and to prevent them from developing from the saprophytic to pathogenic forms ; our task is to help Nature in every way to prevent this dangerous transformation of the filtrable virus or the saprophytic bacillus to the acid-fast form. This may be achieved by the avoidance of all debilitating occupations, by improving living conditions, by proper and sufficient feeding, a return to country life, and the avoidance of urban life with its dangers of overactivity and intoxication ; by developing healthy habits, ensuring good sanitation in the home, and above all by attacking alcoholism, which causes hundreds of persons yearly to become confirmed consumptives, persons who might have overcome their heredity were it not for this indulgence.

Over a period of twenty years, in Lyons, alcoholism has been responsible for 4,000 deaths from tuberculosis ; this figure has counterbalanced the decline in the death-rate from the disease which would otherwise have been apparent.

I think we are also justified in placing some reliance on therapeutic measures. Although no specific remedy has yet been found for tuberculosis, the combination of artificial pneumothorax treatment with chrysotherapy, and with attentive and sustained therapeutic measures designed to ensure the normal operation of all organic functions, is calculated to arrest the progress of the disease, to encourage remissions and to improve the condition of the patient in the vast majority of cases.

But this is a problem in itself. I only wish to point out that we are not devoid of weapons against tuberculosis. But while we are waiting for the discovery of the perfect remedy—if it is ever to be discovered—we must try not to be led astray by some useless prophylactic measure, ignoring the more promising resources which are already available.

APPENDIX I.

REPLIES TO CRITICISMS.

I hope I may be permitted to reply to certain criticisms which have been directed, not against my argument itself, but against the means I have used to investigate this problem. These criticisms have chiefly been levelled at my clinical competence and working methods.

(a) *Competence.*

In an article published in *Progress* of July 31, 1930, "Hippocrates" (whom I must refer to by this pseudonym as I do not know his real name) contends that my investigations have been confined to pharmaceutical chemistry and theoretical biology. To make this criticism he had to seek the opinion of certain eminent medical men, authorities on respiratory diseases, who have attended thousands of cases of tuberculosis and have acquired an experience which a laboratory chemist naturally cannot be expected to have, or so he says.

"In order to understand tuberculosis," he writes, "a man must have visited many tenement homes, and have listened to the tragic stories which are confided only to a general practitioner."

The fact that I have never been a general practitioner apparently leads "Hippocrates" to tax me with clinical incompetence. Does he believe I am so rash? How impudent it would have been to engage in such an important controversy without being thoroughly competent to do so from the clinical point of view.

For many years I have been examining tuberculous cases and collecting observations, which I have recorded with the utmost care; these observations have been made either on the out-patients attending my laboratories or on patients in the hospital wards, to whom I have access. I have gathered my information, not by visiting tenements, it is true, but by filing hundreds of records and drawing up as exact an account as possible of all my cases, some of which I have examined more than fifty times; these records include radiographs, often several for each case, and all sorts of analyses, as well as radiological and clinical investigations relating to the parents of the patient. And the whole of this mass of information has been collected without interruption by the

claims of practice (since I am not a general practitioner), without financial hindrance, and without need to consider the expense incurred by the patients—for I undertook the charges myself. Some idea of what this means may be formed from the fact that I had over five hundred radiographs taken of patients in the course of the year 1930 alone. I have aimed purely at scientific research and the pursuit of truth.

I have prepared my clinical records with a scrupulousness which has probably never been brought to the same task by any other investigator.

What observer has produced statistics showing that the heredity of patients has been systematically investigated by auscultation, radioscopy and radiography of their parents? I have looked for examples in vain. Yet how can we rely on information which is based on inadequate data?

Surely my clinical work, carried out under unusually favourable conditions, deserves to be taken into consideration and does not justify such derogatory and unsubstantiated criticism.

Readers will be able to judge whether the practitioner who climbs flights of tenement stairs but has perforce to be content with a cursory examination and an inaccurate history supplied by the patient, has any advantage over an observer who is not satisfied until he has had the opportunity of investigating the patient's heredity by every method which science can place at his disposal.

According to my friend Prof. CALMETTE, however, the boot is on the other foot. He blames me for falling short in quite a different direction. In his opinion my laboratory experiments are inadequate because I have been unable to ascertain what takes place in large animals, especially the bovidæ, and am consequently unqualified to frame a judgment on the problem of tuberculosis.

It is true that I cannot compare my own laboratory work with the grand experiment upon a large scale which my eminent friend has had the opportunity to pursue—an opportunity such as I am never likely to encounter, since I depend entirely upon my private resources to carry out my work. These resources, however, have proved sufficient to enable me to build and fit up laboratories which, as a private enterprise, are probably unique in France.

The buildings cover an area of over 3,000 square metres, and comprise eighty rooms divided into three departments: chemical, physiological and clinical. For nearly thirty years I and my ten colleagues have been at work there. The investigations which we have been able to pursue during that time are considerable, and from them we have been able to form precise opinions upon the ætiology, pathogenesis and characteristics of experimental tuberculosis.

We have certainly not had large animals or apes at our disposal, but have had to be content with domestic animals and guinea-pigs.

If I wished to cry *tu quoque*, I might point out to my critic that, as regards heredity and still more as regards infection, between man and animals, the organic differences, the differences in tissue fluids and of reaction in various species, the differences of habitat, habits, customs and food—in a word, the differences in the conditions of life are so wide *that it is really not permissible to apply to the human species conclusions drawn from experiments made on cows or even on apes*.

Needless to say, I do not deny the importance of animal experiments, but care should be taken not to generalise from them, and especially not to apply to one animal species facts which have been ascertained upon another.

The following observation will prove my point :—

We are told by observers that if a tuberculous cow is introduced into a stable it will infect its neighbours. But if, on the other hand, we place a tuberculous guinea-pig among other animals of the same species, it will not infect any of them; and yet it is a matter of general knowledge that the guinea-pig is highly susceptible to tuberculosis under conditions of experimental inoculation.

A guinea-pig living in a tuberculous environment will never become infected.

Furthermore, while I have not been able to perform experiments on large animals, I am well informed about the investigations which have been made by various observers in this field, and I have not failed to take their results into account. My critics themselves did not perform all the experiments which they quote.

Moreover, and this is a point I wish to emphasise, conditions of life have a greater influence upon tuberculous infection than the susceptibility of the species, the virulence of the organism or the nature of the medium. The comparison mentioned above, between the cow and the guinea-pig, makes this clear. If, therefore, we are anxious to learn something about the part played by infection in relation to the human species, it is in man that we should investigate it: clinical observations are more valuable than experiments with animals; such animal experiments can have little significance since the factors that control infection in men and animals are essentially different, and not in the least comparable.

The most serious criticism which could be made of an observer working on the subject of tuberculous infection occurring between adult men would be to suggest that he had omitted to inquire into the conditions found in human subjects, and I have recognised this so fully that I have pushed my clinical

investigations as far as possible, and have refused to limit them to those superficial examinations with which most practitioners have had to content themselves.

I believe this explanation will make it clear that my opponents have charged me with incompetence only because they were misinformed about my work and about the care and the conscientiousness with which it has been performed.

(b) *Scientific Method.*

Let me remind readers that I was reproached by the writer going by the name of "Hippocrates" with not having put my theory to the test of a public medical discussion :—

"M. LUMIÈRE is a member of the Académie de Médecine. One cannot help being surprised that, before imparting his ideas to the general public, who know nothing at all about it, he did not place them before his colleagues. They would certainly have provoked an interesting debate and, for once, the Académie de Médecine would have proved of some use."

Let me quote what a member of the Académie recently wrote to me :—

"I have read your views upon the inheritance of tuberculosis and the questions which it raises. One of these days the matter will have to be laid again before the Académie and fully dealt with. Your book will have helped to throw some light upon it."

In reply to "HIPPOCRATES" I may say that my book is not a novel for general entertainment, but a medical book intended for medical men, and that I preferred to address the whole body of practitioners rather than the group of persons (highly distinguished it is true, but limited in number) who constitute the Académie. I consider that the problems of tuberculosis cannot be solved by speeches, which too often have an unfavourable influence on the trend of medical thought.

It must be realised that in an assembly, even an assembly composed of learned members, success will on most occasions attend, not the man who is in the right, but the man who proves the most eloquent. Charm of delivery, telling phrases, a knowledge of mass psychology are factors which disturb the judgment of an assembly called upon to give an opinion.

If a speaker in an academic controversy quotes in support of his thesis some fact which his opponent has misunderstood or disregarded, in most cases it is impossible for the opponent to defend his position because the analysis of such a fact, and an investigation into its origin or significance, could not be carried out all in a moment; the evidence would have to be examined at leisure, and not in the controversial atmosphere of the Académie.

The French Académie de Médecine represents the accepted views of the medical profession; for many years its members

have unanimously held that tuberculosis is always transmitted by infection; the present generation has come to regard this view as a sort of religious tenet, and religions hardly admit of reasoning and discussion. Before any attempt is made to get them to relinquish this creed the idea must be introduced that the conventional theory is open to discussion and ought to be discussed; and that no one is entitled to make a creed of it—it must only be regarded as a hypothesis.

Inquiry into this hypothesis must be resumed with greater accuracy than in the past; the variable factors must be taken into account, and some idea must be formed of their relative values; all this must be performed dispassionately and without bias or prejudice in favour of a previous opinion. These are all difficult things to obtain.

The task requires time and forbearance, I know. But I have sufficient patience not only to set out the reasons which led me to attack the prevailing theory, but to correct my own errors and amend my present views—which may still be remote from scientific truth.

This is a question which, because of its extreme complexity, has remained in the balance for centuries, a question upon which the Académie has repeatedly expressed the opposite view to mine. Am I expected to ask the Académie to dispose of the subject finally in a few hours? A nice reasonable suggestion I must say.

Only one course seems to be open to me: to set to work again, to resume the investigation of infection and heredity in tuberculosis with more precision, deliberately bringing any powers I may have of analysis and criticism to bear on the question; such critical qualities, as I think I have shown, have not always been brought to the task of collecting and interpreting the information upon which the conventional theory is founded.

This is my main object in publishing communications upon tuberculosis.

Again I have been charged with basing my statements on statistical returns, such returns rarely being trustworthy.

“HIPPOCRATES” wrote: “The most serious criticism we have to make of M. LUMIÈRE is that he has trusted to statistics.” To make such a statement he must have read my book very superficially.

I am as well aware as anyone else of the weak points of demographical returns and, in certain of my publications (notably those relating to cancer problems), I have repeatedly criticised the inadequate methods upon which statistical returns are usually compiled in this country. And that is why I have always been cautious in making use of them.

I have had to refer to them, however, in order to elucidate certain points in my investigation, since, apart from this informa-

tion, I had nothing upon which to base my arguments. Whenever I have found it necessary to make use of demographical returns, I have always made allowances for a certain coefficient of approximation in the more reliable of such returns, and have determined the degree of error in the others.

Did I not show the extreme differences in the estimates, made by various observers of the incidence of conjugal tuberculosis—those estimates being based upon statistics? One of these observers estimated the incidence of conjugal infection at 2.20 per cent., while another put it at 58 per cent.

I ascribed those almost incredible discrepancies to the degree of care with which the different observers sought for the hereditary factor, and I pointed out that these investigations ought to be resumed under conditions which would permit of comparison.

In addition, reference to statistics has only been necessary for a portion of my argument. I have drawn the essential elements from clinical and experimental observations.

On the other hand, I have relied in detail upon statistics compiled by myself; I am aware of the weak points of such statistics, and consequently can make legitimate use of them.

For example, I have quoted statistics which I compiled myself relating to the mortality from tuberculosis in Lyons over a period of twenty years; to collect these statistics I examined personally the 188,000 death certificates upon which the information was based, and interpreted and classified them according to a definite system; I am perfectly aware, therefore, that although I cannot regard the death-rate from tuberculosis reckoned as a percentage of the total number of deaths as strictly accurate (since the cause of death given on the death certificate is often inaccurate or vague), I may nevertheless draw certain valid inferences from these statistics with regard to the differences of mortality in the two sexes, since the degree of error will be the same in both cases.

Similarly, when I refer to my own statistics relating to conjugal tuberculosis, I know within what limits I can rely on them, since I know in which cases I have been able to investigate the hereditary factor thoroughly, and in which the investigation was not sufficiently adequate to justify an expression of opinion.

In short, I have based my opinion chiefly on clinical investigations, partly on laboratory research, and only to a small extent upon statistics.

My clinical investigations were especially directed towards a search for the hereditary factor in the parents of tuberculous cases. The fact that my attention was directed to a single definite purpose may, perhaps, explain why I have placed more emphasis on strict accuracy than other observers have done.

My own laboratory experiments have been extensive, but I have also paid considerable attention to those appearing in the literature upon tuberculosis.

In short, I have only taken from statistics those points which were of value to my argument. After all, even statistics contain some elements of value. They have been abused, but that is no reason why they should not be used properly; in evidence of which I may point out that statistics have been used to determine the value of B.C.G.

Nor has there been any hesitation about quoting statistics in order to refute my arguments, so why should I be criticised for using the same sources of information, when I have always been careful to estimate their accuracy, and to make allowance for errors?

I hope I have given a sufficient answer to those critics who, before examining the merits of my work, saw fit to question both my competence and the accuracy of my methods.

APPENDIX II.

CONJUGAL INFECTION STATISTICS.

Statistical Return of the last 169 Cases investigated.

Negative Cases.

Mrs. Ro., died aged 53 from pulmonary tuberculosis. One son with bilateral fibro-caseous lesions.	Husband, aged 63, unaffected.
Mr. Sar., fibrous tuberculosis for the last thirty years. One son died from consumption. A sister died from meningitis. Another son has extensive bilateral fibro-caseous lesions.	Wife, aged 66, unaffected.
Mrs. Sau., fibro-caseous lesions for many years. One tuberculous son.	Husband unaffected; died aged 64 from cancer.
Mr. Sau., son of preceding, aged 45, consumptive for the last four years. Extensive lesion on the right side. Tubercle bacilli in sputum.	Wife unaffected.
Mr. Sau., died aged 58. Extensive bilateral lesions. Termination, caseous pneumonia. Large numbers of tubercle bacilli in sputum.	Wife unaffected.
Mr. Tou., aged 45. Fibrous lesions of both apices. Emphysema.	Wife unaffected.
Mr. Tas., aged 24. Fibro-caseous lesion of right apex. Tubercle bacilli in sputum.	Wife unaffected.
Mr. Tru., aged 54. Extensive fibro-caseous bilateral lesions. Tubercle bacilli in sputum for several years.	Wife unaffected.
Mr. Val., died aged 74, bronchitic for the last thirty years. One tuberculous son.	Wife, aged 75, unaffected.

Mr. Val., son of the preceding, aged 55. Bilateral fibrous tuberculosis. Emphysema.	Wife unaffected.
Mr. Man., aged 31. Fibro-caseous lesion of right apex. Tubercle bacilli in sputum.	Wife unaffected.
Mr. Mas., chronic bronchitis for the last twenty years. Emphysema. One son with analogous lesions and symptoms.	Wife unaffected.
Mrs. Mar., died from tuberculosis, aged 40. One tuberculous son.	Husband unaffected.
Mrs. Mon., died from chronic bronchitis aged 38. One consumptive son. Fibro-caseous lesion of right apex.	Husband unaffected.
Mr. Mon., son of preceding, aged 51. Fibro-caseous lesion of right apex. Tubercle bacilli in sputum.	Wife unaffected.
Mrs. Mic., died from bronchitis ten years ago. One tuberculous son.	Husband unaffected.
Mr. Mic., son of the preceding, aged 40. Fibrous-caseous lesion of right apex. Tubercle bacilli in sputum.	Wife unaffected.
Mr. Mio., aged 47, bronchitic for the last twenty years, fibrosis. One tuberculous son. Caries of bone.	Wife, aged 47, unaffected.
Mr. Past., died aged 46 from tuberculous laryngitis. One tuberculous son.	Wife unaffected.
Mr. Past., aged 31, son of preceding. Bilateral fibrosis.	Wife unaffected.
Mr. Pil., died aged 64 from tuberculosis. One son aged 30. Fibrous tuberculosis.	Wife unaffected.
Mr. Pos., died aged 55. Consumptive. One tuberculous son aged 26. Bilateral lesions.	Wife unaffected.

Mr. Ray., died aged 28 from tuberculous laryngitis. One tuberculous son aged 29.

Wife, aged 55, unaffected.

Mr. Roc., bronchitic for the last forty years. One son died from tuberculosis. Another son attacked with bilateral fibro-caseous lesions.

Wife unaffected.

Mr. Roc., son of preceding, aged 38. Extensive fibro-caseous tuberculosis. Tubercle bacilli in sputum.

Wife unaffected.

Mr. Rol., aged 42. Right apex fibrous for the last ten years.

Wife unaffected.

Mr. Gac., alcoholic, tuberculous, died from purulent pleurisy. One tuberculous son.

Wife unaffected; died at ninth confinement.

Mr. Gac., son of preceding, aged 61. Fibro-caseous lesion of right apex. Tubercle bacilli in sputum.

Wife unaffected.

Mr. Ga., alcoholic. Tuberculous laryngitis. The father died of tuberculosis. One tuberculous child.

Wife unaffected.

Mrs. Ku., old chronic bronchitis. Two tuberculous sons.

Husband unaffected; died from acute pneumonia.

Mrs. Ch., died aged 58 from generalised tuberculosis. Two children who died from meningitis.

Husband, aged 72, unaffected.

Mr. W., died of consumption aged 34. One son. Fibrous tuberculosis.

Wife unaffected; died in accident twenty years later.

Mrs. La., died from tuberculosis aged 55. Two tuberculous sons. One grand-daughter died from tuberculosis.

Husband, aged 64, unaffected.

Mrs. Se., died from acute tuberculosis aged 26.

Husband unaffected; died twenty-five years later.

Mr. Pa., died from cancer aged 55, but suffered from fibrous tuberculosis. One tuberculous son.	Wife unaffected.
Mr. Pa., son of preceding. Died aged 33 from generalised tuberculosis.	Wife unaffected ten years afterwards.
Mr. La., aged 77, bilateral fibrosis. One brother with same lesions.	Wife unaffected.
Mr. Ca., died from tuberculosis aged 68. One tuberculous son.	Wife unaffected.
Mr. Ca., son of preceding. Fibro-caseous lesion of right apex. Tubercle bacilli in sputum.	Wife unaffected.
Mr. Ba., chronic bronchitis, pleurisy. One tuberculous daughter.	Wife unaffected.
Mrs. Via., daughter of preceding, aged 22. Extensive bilateral fibro-caseous lesions.	Husband unaffected.
Mrs. Za., tuberculous, died from complications following influenza in 1918. Two tuberculous daughters.	Husband unaffected twelve years later.
Mr. An., died tuberculous aged 42. One son and one grandson tuberculous.	Wife, aged 68, unaffected.
Mr. An., son of preceding, aged 37. Fibrosis of both apexes. One tuberculous son.	Wife unaffected.
Mrs. Ba., aged 41. Fibro-caseous lesion on right. Tubercle bacilli in sputum. One son Pott's disease and pulmonary tuberculosis.	Husband unaffected.
Mrs. Bl., died aged 60 from chronic bronchitis. One tuberculous son.	Husband unaffected. Died from cancer aged 67.
Mr. Bl., died tuberculous aged 51. One tuberculous son aged 18.	Wife unaffected.

Mrs. Bol., aged 42. Old Pott's disease. One son, aged 18, consumptive.	Husband unaffected; killed during the War in 1918.
Mr. Bo., aged 48. Bilateral fibrous tuberculosis. One son, aged 15, bilateral pulmonary tuberculosis.	Wife unaffected, aged 45.
Mr. Br., aged 72. Bilateral fibrosis. Emphysema. One tuberculous son.	Wife unaffected.
Mr. Re., aged 45. Pleurisy at 17. Chronic bronchitis. One son aged 17. Lesion of left apex.	Wife unaffected.
Mrs. Rou., died consumptive aged 45. One daughter aged 25, bilateral tuberculous lesions.	Husband, aged 61, unaffected.
Mr. Sa., died aged 59. Tuberculous laryngitis. One daughter, aged 29, consumptive.	Wife unaffected, aged 65.
Mr. Si., aged 42. Fibrous bilateral pulmonary tuberculosis of long standing. One son, aged 15, consumptive.	Wife unaffected.
Mrs. Tes., died aged 32. Tuberculous peritonitis. One daughter, aged 21, consumptive. Fibro-caseous lesion of left apex.	Husband unaffected.
Mrs. Tu., aged 67. Long-standing chronic bronchitis. Emphysema. One daughter aged 41. Right apex with fibro-caseous lesions.	Husband, aged 77, unaffected.
Mr. Vac., died aged 52. Tuberculous laryngitis. One daughter, aged 28, fibrosis.	Wife, aged 66, unaffected.
Mr. Val., died aged 66. Chronic bronchitis. One bronchitic brother. One daughter, aged 56, bilateral fibrosis.	Wife, aged 88, unaffected.
Mr. Mer., died aged 44. Chronic bronchitis, diabetes, gangrene. One daughter, aged 53, bilateral fibrosis.	Wife, aged 80, unaffected.

Mr. Vi., aged 62, pleurisy, chronic bronchitis. One daughter, aged 37, consumptive.

Wife, aged 58, unaffected.

Mr. Mi., died aged 53. Tuberculous. Six children who all died from meningitis. One daughter, aged 31, fibro-caseous lesions of right apex.

Wife unaffected.

Mrs. Min., died aged 44. Consumptive. One daughter, aged 34, fibrous right apex.

Husband, aged 64, unaffected.

Mrs. Mo., aged 55. *Renal tuberculosis*. One daughter, aged 33, with *renal tuberculosis*. A sister, *renal tuberculosis*.

Husband unaffected. (Murdered.)

Mrs. Mo., died aged 53, consumptive. One daughter, aged 32, bilateral tuberculous lesions.

Husband, aged 58, unaffected.

Mrs. Na., aged 46. Old fibrous tuberculosis. One daughter, aged 11, with lesions of right apex.

Husband unaffected died aortic aged 50.

Mr. Pa., died aged 48. Alcoholic cirrhosis, consumptive. One daughter, aged 22, lesion of right apex.

Wife, aged 53, unaffected.

Mr. Pa., died aged 50. Tuberculous laryngitis. One son, aged 35, tuberculous. One daughter died consumptive aged 22.

Wife unaffected.

Mrs. Po., died consumptive aged 38. One daughter, aged 24, emphysema, fibrosis.

Husband unaffected, aged 48.

Mr. Ja., aged 60. Long-standing chronic bronchitis. One daughter, aged 32, lupus.

Wife unaffected.

Mrs. Lac., aged 40. Chronic bronchitis. One daughter, aged 19, lesion of right apex.

Husband, aged 45, unaffected.

Mr. Laf., aged 46. Alcoholic consumptive. One daughter, aged 23, extensive lesion of left apex.	Wife unaffected, aged 44.
Mr. Lan., died from tuberculosis aged 35. Daughter, fibrous lesion, left apex.	Wife, aged 57, unaffected.
Mrs. Len., aged 50, tuberculous. Two tuberculous daughters.	Husband, aged 52, unaffected, alcoholic.
Mr. Le., died aged 32 from galloping consumption. One daughter, aged 48, fibrous tuberculosis.	Wife, aged 72, unaffected.
Mrs. Mor., renal tuberculosis, chronic bronchitis, aged 72. One consumptive daughter, aged 32, deceased.	Husband, aged 78, unaffected.
Mrs. Mi., died from tuberculosis aged 35. One daughter, aged 24, bilateral fibro-caseous lesions.	Husband, aged 55, unaffected.
Mrs. Ch., aged 50, tuberculosis detected by radiography. One daughter died from tuberculosis aged 20.	Husband, aged 54, unaffected.
Mrs. Ch., died consumptive aged 40. One daughter, aged 53, bilateral fibrosis.	Husband, aged 76, unaffected.
Mrs. C., died aged 56, chronic bronchitis. One daughter, aged 41, fibrosis right apex.	Husband, aged 66, unaffected.
Mr. Dor., aged 44, fibrous tuberculosis for over twenty years. One daughter, aged 21, fibro-caseous lesion of left apex.	Wife, aged 43, unaffected.
Mr. Con., aged 45, tuberculous. One daughter, aged 21, right apex fibrous.	Wife, aged 48, unaffected.

Mr. Dev., aged 49, fibrous consumptive for the last fifteen years. One daughter, aged 20, fibro-caseous left apex.

Wife, aged 44, unaffected.

Mr. Es., aged 40, consumptive. One daughter died from meningitis. One daughter, aged 17, extensive lesion of left apex.

Wife, aged 39, unaffected.

Mr. F., aged 46, fibrous tuberculosis the last thirty years. Hæmoptysis. Three tuberculous daughters.

Wife, aged 45, unaffected.

Mr. Ba., aged 52, fibrous tuberculosis. One daughter, aged 32, extensive lesion on the left.

Wife, aged 49, unaffected.

Mr. Ber., died aged 55, consumptive. One daughter, aged 39, ulcero-caseous lesion, right apex.

Wife, aged 66, unaffected.

Mrs. Bi., aged 56, chronic bronchitis. One daughter, aged 31, fibrosis.

Husband, aged 59, unaffected.

Mrs. Bi., died tuberculous aged 28. One daughter, aged 23, marked enlargement of cervical glands.

Husband unaffected, aged 49.

Mr. Bl., died tuberculous aged 60. One daughter fibrous tuberculosis.

Wife died aged 86, unaffected.

Mrs. Bl., died tuberculous aged 57. One daughter, aged 48, bilateral fibro-caseous lesions.

Husband died aged 76, unaffected.

Mrs. Boi., died tuberculous aged 57. One daughter, emphysema, fibrosis.

Husband unaffected.

Mr. Bor., died tuberculous aged 45. Daughter, tuberculosis, right apex.

Wife unaffected; committed suicide.

Mr. B., died tuberculous aged 45. One son, lesion of left apex.

Wife unaffected, aged 75.

Mr. Ch., bronchitic, aged 48. One daughter, aged 22, bilateral lesions.

Wife unaffected, aged 44.

Mr. The., died aged 40, tuberculous. One son, emphysematous, aged 49.	Wife unaffected ; died aged 72.
Mr. Thi., died tuberculous aged 43. One son, aged 22, tuberculous.	Wife, aged 60, unaffected.
Mr. Va., died tuberculous aged 44. One daughter, aged 29, phthisis with cavitation.	Wife unaffected.
Mrs. Vi., aged 45, lesion of right apex. One son, aged 16, tuberculosis.	Husband unaffected.
Mrs. Raf., aged 62, chronic bron- chitis. One tuberculous daughter, bilateral lesions.	Husband unaffected.
Mrs. Ra., died tuberculous aged 45. Two tuberculous daughters.	Husband unaffected ; killed during the war in 1918.
Mrs. Re., aged 61, old chronic bron- chitis. One daughter, lesion left apex.	Husband unaffected, aged 64.
Mr. Ri., died tuberculous aged 45. One daughter, aged 41, extensive bi- lateral lesions.	Wife unaffected.
Mrs. Ro., died aged 42, galloping consumption. A brother died tuber- culous. One daughter, aged 37, exten- sive tuberculous lesions.	Husband unaffected ; died accidentally.
Mr. So., aged 40, chronic bronchitis. One son, fibrous left apex.	Wife unaffected.
Mrs. Ph., bronchitic, aged 46. One daughter, aged 25, bilateral fibro- caseous lesions.	Husband unaffected.
Mrs. Pa., daughter of preceding, aged 25, both apexes fibro-caseous.	Husband unaffected.
Mrs. Pe., aged 65, chronic bronchitis. One son died from meningitis aged 16. Another son, aged 40, lesion of right apex.	Husband unaffected.

Mrs. Per., aged 42, bronchitic. Two tuberculous daughters.	Husband, aged 46, unaffected.
Mr. Pe., aged 66, bronchitic. One daughter, aged 40, tuberculous.	Wife unaffected.
Mrs. Po., died aged 42, tuberculous. One son, ulcerous tuberculosis.	Husband, aged 82, unaffected.
Mr. Po., died aged 50, old bronchitis, pleurisy. One tuberculous son aged 42 years.	Wife, aged 69, unaffected.
Mr. Pu., died tuberculous aged 64. One tuberculous daughter aged 24.	Wife unaffected.
Mrs. Qu., daughter of preceding, aged 24. Extensive tuberculous lesion left apex.	Husband unaffected.
Mr. Men., died from bronchitis aged 58. Seven bronchitic children.	Wife unaffected ; died from heart disease when aged 58.
Mr. Met., died from tuberculosis aged 46. One daughter died consumptive aged 38.	Wife unaffected ; died from cancer aged 58.
Mr. Mou., died from tuberculosis aged 39. One daughter, aged 37, tuberculous.	Wife, aged 70, unaffected.
Mr. Mo., fibrous tuberculosis left apex. One daughter, aged 24, tuberculous.	Wife unaffected.
Mrs. M., died from tuberculosis aged 42. One daughter, aged 33, consumptive. Extensive bilateral lesions.	Husband unaffected ; died aged 60 from cancer.
Mrs. Mou., died tuberculous aged 21. One son, aged 40, consumptive.	Husband unaffected ; died aged 57 from cirrhosis of the liver.
Mrs. Cl., died from chronic bronchitis at 57. One son, aged 34, consumptive.	Husband unaffected ; died aged 64. Fit.

Mrs. Or., died consumptive aged 22.	Husband unaffected ; died from cancer aged 57.
Mrs. Gr., died aged 56. Chronic bronchitis.	Husband unaffected ; killed accidentally.
Mrs. La., died consumptive aged 47. One daughter, aged 31, tuberculous.	Husband unaffected ; died in old age from cancer.
Mrs. Ma., died tuberculous aged 36. Three children died from tuberculosis. Another daughter consumptive.	Husband unaffected.
Mr. Mar., died aged 53, bronchitis. One son consumptive.	Wife unaffected.
Mr. Ma., aged 48, chronic bronchitis. One son, aged 24, consumptive.	Wife unaffected, aged 47.
Mr. Em., died aged 57, meningitis. One consumptive daughter. <i>Seven brothers and sisters died from meningitis.</i>	Wife unaffected ; died when aged 37 after being delivered of her eighth child.
Mrs. Fa., chronic bronchitis. One son and one daughter tuberculous.	Husband unaffected ; died aged 64, hemiplegia.
Mr. Fau., died tuberculous aged 42. One son, aged 15, consumptive.	Wife, aged 56, un- affected.
Mr. Fr., pleurisy and lesion of left apex. One son with marked enlarge- ment of cervical glands.	Wife unaffected.
Mr. Ga., aged 64, chronic bronchitis. One son consumptive.	Wife, aged 61, unaffected.
Mrs. Gi., aged 38, tuberculous. A son and a daughter both tuberculous.	Husband unaffected, aged 40.
Mr. Co., aged 50, chronic bronchitis. A son, Pott's disease. A daughter, fibrosis.	Wife unaffected.

Mrs. Dar., died aged 42, galloping consumption. A daughter, fibrosis. Another daughter died consumptive aged 22.

Husband, aged 73, unaffected.

Mrs. Da., died consumptive aged 46. A tuberculous son aged 25.

Husband unaffected.

Mrs. Dol., at the age of 20 developed chronic bronchitis which lasted three years. One son, aged 15, with lesion left apex.

Husband, aged 46, unaffected.

Mr. Del., died of tuberculosis aged 48. One daughter, aged 32, lesion of right apex.

Wife, aged 62, unaffected.

Mr. Duc., chronic bronchitis for the last fifteen or twenty years. A tuberculous daughter.

Wife unaffected.

Mrs. Duc., aged 46, chronic bronchitis since she was 10. Two infants died early from meningitis. A tuberculous daughter.

Husband unaffected; died from heart disease when aged 42.

Mr. Cil., died aged 58, tuberculous alcoholic. One daughter, aged 18, tuberculous. A tuberculous brother.

Wife unaffected.

Mr. Ch., died aged 48, cirrhosis and bacillosis. One tuberculous son.

Wife, aged 68, unaffected.

Mrs. Cin., died of tuberculosis aged 50. One consumptive daughter aged 32.

Husband, aged 56, unaffected.

Mr. Ab., died of tuberculosis aged 36. A tuberculous son aged 6.

Wife unaffected.

Mrs. Al., bronchitic. One tuberculous daughter.

Husband unaffected.

Mr. An., aged 44, emphysema, chronic bronchitis. Right apex involved. One son, aged 6, left apex involved. Another son died from meningitis.	Wife, aged 40, unaffected.
Mr. Bas., died aged 36, Pott's disease. One daughter, aged 36, consumptive. Right apex involved.	Wife, aged 54, unaffected.
Mr. Bar., aged 40. Chronic bronchitis. One son, aged 16, tuberculous.	Wife unaffected.
Mrs. Bi., died tuberculous aged 34. One son, aged 17, tuberculous.	Husband unaffected.
Mrs. Bo., died of tuberculosis aged 42. A daughter, aged 16, tuberculous.	Husband unaffected.

In considering the above series it should be borne in mind that it was not possible to examine and X-ray the husband or wife of the patient in every case, so that a certain number of those stated to be unaffected were probably tuberculous.

On the other hand, in contrast to this series of 150 in which only one partner was attacked, I am able to record only 19 cases in which both husband and wife were tuberculous.

Cases in which both Husband and Wife were tuberculous.

Mr. and Mrs. Bed.; died aged 47 and 42. One tuberculous daughter.	?
Mr. and Mrs. Bo.; both living, both bronchitis. One tuberculous daughter aged 17.	Both come of tuberculous stock.
Mr. and Mrs. Bon. Husband under treatment. Wife has had pleurisy. One son died consumptive.	Both come of tuberculous stock.
Mr. and Mrs. Bu. Husband bronchitic. Wife alcoholic, bronchitic. Three tuberculous children.	Both come of tuberculous stock.

Mr. and Mrs. Ca. Father living, bronchitic. Mother died of tuberculosis aged 22. One daughter, Pott's disease. Another daughter, tuberculosis.

?

Mr. and Mrs. Du. Husband chronic bronchitis, hæmoptysis. Wife tuberculous. A son, Pott's disease.

Both come of tuberculous stock.

Mr. and Mrs. Dus. Husband with pleurisy. Wife chronic bronchitis. One son, aged 7, emphysema.

A history of tuberculosis in both families.

Mr. and Mrs. Le. Husband tuberculous laryngitis. Wife, pleurisy. Son, tuberculous.

?

Mr. and Mrs. Mi. Husband found unfit for military service on account of bronchitis. Wife, chronic bronchitis. Two tuberculous sons.

?

Mr. and Mrs. Mu. Husband emphysema, fibrosis. Wife chronic bronchitis. One asthmatic son.

?

Mr. and Mrs. Pe. Husband, aged 40, bronchitis. Wife, aged 42, pleurisy. One daughter, aged 14, tuberculous.

Both come of tuberculous stock.

Mr. and Mrs. Sa. Husband, aged 52, bronchitis. Wife, aged 50, tuberculous. One son, aged 15, tuberculous.

?

Mr. and Mrs. Mi. Husband and wife, bronchitis. A daughter died from meningitis. Another, aged 27, lesion right apex.

Both come of tuberculous stock.

Mr. and Mrs. Ti., husband and wife, both bronchitic. Died aged 42 and 43. One daughter. Fibrosis at right apex.

Both come of tuberculous stock.

Mr. and Mrs. Fr. Husband, aged 46, chronic bronchitis. Wife, aged 46, pleurisy. One tuberculous son.

?

Mr. and Mrs. Ch. Husband died aged 57, galloping consumption. Mother, aged 58, bronchitic. One son, aged 23, tuberculous. ?

Mr. and Mrs. Ig. Husband died aged 47, galloping consumption. Wife, chronic bronchitis. ?

Mr. and Mrs. En. Husband died aged 36, tuberculous. Wife bronchitic. Two tuberculous children. Both come of tuberculous stock.

Mr. and Mrs. To. Husband alcoholic consumptive. Wife emphysema, fibrosis. ?

I was able to trace a tuberculous family history on both the husband's and on the wife's side in nine of these married couples. In the ten remaining cases I have been unable to obtain sufficient particulars.

An examination of the cases quoted here precludes the idea of conjugal infection. At most it can be asserted that if conjugal infection occurs at all it must be very rare.

Out of the 169 couples under consideration, 148 have become the parents of tuberculous children, the total number of such children amounting to 187. There are only 21 couples whose children are at present unaffected. Of this series of 21 couples some are childless and others are still so young that it is impossible to foreshadow the fate of their children.

A certain number of the children of the 169 couples in the series have not yet reached the age at which tuberculosis most frequently appears, so that the high incidence of tuberculosis among members of the rising generation must be regarded as an underestimation.





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