Transactions

of the

Sixth International Congress on Tuberculosis.

WASHINGTON, SEPTEMBER 28 TO OCTOBER 5, 1908.

WITH AN ACCOUNT AND CATALOGUE OF THE TUBERCULOSIS EXHIBITION,

WASHINGTON, SEPTEMBER 21 TO OCTOBER 12, 1908.

In Six Volumes.

VOLUME ONE, PART ONE.

PROCEEDINGS OF SECTION I,
Pathology and Bacteriology.

PROCEEDINGS OF JOINT SESSION OF SECTIONS I AND II,
Opsonic Index. Conjunctival and Cutaneous Tuberculin Reactions. Serum Diagnosis.

Philadelphia:
WILLIAM F. FELL COMPANY
1908.

EDITED BY THE SECRETARY-GENERAL.

COMMITTEE ON PRINTING AND PUBLICATION.

Dr. Livingston Farrand, Chairman.
Mr. Homer Folks.
Dr. H. R. M. Landis.
Dr. John H. Lowman.
Dr. Marshall L. Price.
Dr. Joseph Walsh.

EDITORIAL COMMITTEE.

The Presidents of the Sections.
Dr. Wm. H. Welch.
Dr. Vincent Y. Bowditch.
Dr. Charles H. Mayo.
Dr. Abraham Jacobi.
Mr. Edward T. Devine.
Surgeon-General Walter Wyman.
Dr. Leonard Pearson.

EXECUTIVE COMMITTEE.

Dr. Lawrence F. Flick.
Dr. Livingston Farrand.
Dr. Joseph Walsh.
Dr. John S. Fulton.

Officers of Section I.

President:

Dr. William H. Welch.

Honorary Presidents:

Prof. J. George Adami, Montreal,
Dr. Julius Bartel, Vienna,
Dr. Leon Bernard, Paris,
Prof. A. Calmette, Lille,
Prof. Jules Courmont, Lyon,
Dr. Paul Courmont, Lyon,
Prof. J. Denys, Louvain,
Dr. Ladislaus Detre, Budapest,
Dr. Arthur Eastwood, London,
Prof. J. Fibiger, Copenhagen,
Prof. Francis Harbitz, Christiania,
Dr. Carl Hart, Berlin,
Dr. Nicolaus Jancso, Klausenburg,
Dr. G. Kuss, Angicourt, France,
Prof. S. Kitasato, Tokyo,
Prof. M. Letulle, Paris,
Dr. James Miller, Birmingham, England.
Dr. Eduard Rist, Paris,
Prof. A. Rodet, Montpellier,
Prof. C. H. H. Spronck, Utrecht,
Prof. N. Ph. Tendeloo, Leiden,
Prof. R. Tripier, Lyons,
Dr. A. Wolff-Eisner, Berlin,
Prof. Sims G. Woodhead, Cambridge.

Vice-Presidents:

Dr. E. R. Baldwin,
Dr. Stanley P. Black,
Maj. James Carroll,*
Dr. Wm. T. Councilman,
Dr. Edward K. Dunham,
Dr. James Ewing,
Dr. Simon Flexner,
Dr. Ludwig Hektoen,
Dr. Wm. T. Howard, Jr.,
Dr. E. O. Jordan,
Dr. J. J. Kinyoun,
Dr. D. J. McCarthy,
Dr. Joseph McFarland,
Dr. W. G. MacCallum,
Dr. F. G. Novy,
Dr. Wm. Ophüls,
Dr. Wm. H. Park,
Dr. Richard M. Pearce,
Dr. T. M. Prudden,
Dr. M. J. Rosenau,
Dr. Allen J. Smith,
Dr. Richard P. Strong,
Dr. Alonzo E. Taylor,
Dr. V. C. Vaughan,
Dr. A. S. Warthin,
Dr. F. F. Wesbrook,
Dr. C. Y. White,
Dr. H. U. Williams.

Secretaries:

Dr. Harold C. Ernst,
Dr. Wm. Royal Stokes.

* Deceased.

Preface.

In the earliest announcements of the Sixth International Congress on Tuberculosis, the Central Committee expressed the intention to publish full accounts in each of the four official languages. As the program developed, it became quite clear that this ambitious project could not be realized. The task of publication would have been long, laborious, and expensive; and the advantage of availability in four languages would have been far outweighed by the delay in publication. The translations made in advance of the Congress have been fully incorporated in the published proceedings, however, and these will supply part of the value which was sought in the original project to translate in full. These translations were made by the special committee under the chairmanship of Dr. Joseph Walsh, and were distributed to the members of the Congress while in session at Washington. Two hundred and ninety-one papers passed through the hands of this Committee and were available in two or more of the official languages.

Contributors who did not forward copies of their papers early enough to be abstracted and translated before the opening date of the Congress have incurred a disadvantage in that their papers appear in one language only. The Committee on Publication, at the close of the Congress, found itself unable to bear any additional expense on account of abstracting or translation.

The order of the volumes in the present series does not conform to precedent. Volume I contains the proceedings of Section I and Section II, and succeeding volumes continue with the proceedings of the Sections. In this way, the account of the organization, the general sessions, the exhibition, the namen-registers, and the general index are all found in the last volume. Each volume has its own index.

At the end of his task the editor is mindful that there are in these volumes more editorial faults than all the readers are likely to discover. He has had extraordinary pleasure in handling so large and so rich a collection of papers, has done his best, has enjoyed perfect coöperation on the part of the printers, and believes that the Transactions truly record the present status of the universal struggle against tuberculosis.

Contents of Volume I, Section I.

Contents of Volume I, Joint Session of Sections I and II.

Contents of Volume I, Section II.

SECTION I.

FIRST SESSION.

Monday afternoon, September 28th, at half past two o'clock, in the New National Museum.

THE BIOLOGY OF THE TUBERCLE BACILLUS.

Section I of the Sixth International Congress on Tuberculosis was called to order by the president, Dr. William H. Welch, at half past two o'clock on Monday afternoon, September 28th, in the New National Museum.

The following were elected honorary presidents of Section I:

Prof. J. George Adami, Montreal.
Dr. Julius Bartel, Vienna.
Dr. Léon Bernard, Paris.
Prof. A. Calmette, Lille.
Prof. Jules Courmont, Lyons.
Dr. Paul Courmont, Lyons.
Prof. J. Denys, Louvain.
Dr. Ladislaus Detre, Budapest.
Dr. Arthur Eastwood, London.
Prof. J. Fibiger, Copenhagen.
Prof. Francis Harbitz, Christiania.
Dr. Carl Hart, Berlin.
Dr. Nikolaus Jancsó, Klausenburg.
Dr. G. Kuss, Agincourt, France.
Prof. S. Kitasato, Tokyo.
Prof. M. Letulle, Paris.
Dr. James Miller, Birmingham, Eng.
Dr. Eduard Rist, Paris.
Prof. A. Rodet, Montpellier.
Prof. C. H. Spronck, Utrecht.
Prof. N. Ph. Tendeloo, Leyden.
Dr. Pierre Teissier, Paris.
Prof. R. Tripier, Lyons.
Dr. A. Wolff-Eisner, Berlin.
Prof. G. Sims Woodhead, Cambridge, Eng.

OPENING REMARKS BY THE PRESIDENT OF THE SECTION.

DR. WILLIAM H. WELCH,
Baltimore.

I esteem it a high honor and privilege in behalf of my American colleagues to extend a most cordial welcome to all in attendance upon this first section of the Sixth International Congress on Tuberculosis, and especially to those who have come from foreign countries to participate in our proceedings. We are indeed fortunate in the presence of so many distinguished investigators, whose papers and discussions enrich our program and give assurance that this Congress will not pass without substantial contributions to our knowledge of tuberculosis.

It will not be deemed invidious if I express the especial gratification which we all feel in having with us, as an active participant in the work of this Section, his Excellency, Professor Koch, the illustrious discoverer of the tubercle bacillus, who must rejoice to witness, in such a gathering as this, the evidences of the far-reaching and inestimable benefits to mankind which have come from this discovery, and the promise of greater benefits in store. We appreciate most highly the participation of so many eminent colleagues from France, who have coöperated so generously and so effectively in all our efforts toward the success of this Congress. We welcome warmly our kindred in speech and in blood from Great Britain and her possessions, and with equal cordiality our fellow-workers from Germany and Austria-Hungary, from Holland and the Scandinavian countries, from Spain, Russia, and other European countries, from Japan and the Orient, and from our sister republics of Central and South America.

Every effort has been made to assure the truly international character of this Congress, and a glance at our program will indicate that this result has been secured. Over seventy per cent. of the papers on the program of Section I are contributed by participants from foreign countries—a gratifying result made possible by a certain measure of self-restraint on the part of American workers, who were prepared to furnish papers, if the time permitted.

A word concerning the construction of the program of this Section may be of interest. After consultation with other officers of the Section I determined that, instead of selecting themes for discussion and inviting referees and co-referees in accordance with the usual custom, I would accept papers voluntarily submitted and then arrange them in groups with the expectation

that the result would be much the same, and that the more important and larger themes would thus be presented by those actually engaged in their study and whose interest was for the time concentrated upon the subjects presented by them. By thus grouping the titles of papers voluntarily submitted, the larger topics, such as the biology and chemistry of the tubercle bacillus, the channels and sources of infection, the specific tuberculin reactions, immunity, the relations of human and bovine tuberculosis, will be presented in a satisfactory and authoritative manner.

In view of the crowded condition of our program I must remind the readers and discutants of the necessity of strict enforcement of the rules, that the time allotted for referees and co-referees is not to exceed fifteen minutes, for readers of papers ten minutes, and for participants in the discussions five minutes; and especially I would urge the importance of handing to the Secretary of the Section the written remarks in discussion before the close of each meeting in order to secure their appearance in the transactions.

The main significance of the International Congresses of Tuberculosis has been in the past, and will continue to be, on the side of prevention of the disease. As has been said, tuberculosis is indeed the disease of the people, in a truer and larger sense than can be affirmed of any other malady. From the discovery of the tubercle bacillus, and the study of its properties, and of the sources and modes of infection, there has come a new message of hope to suffering humanity, so full of untold blessing that the peoples of the earth have been aroused to its significance, and in all civilized countries there has been inaugurated what is appropriately called the crusade against tuberculosis. Already in certain places the application of intelligent measures of prevention, based upon the new knowledge, has achieved results so full of promise that the hopes of even the most enthusiastic no longer seem so extravagant as they may once have appeared. Nowhere has the existing knowledge been applied to the prevention of tuberculosis save in part and inadequately, but the achievements of even this imperfect application are sufficient to inspire the world to the search for fuller knowledge, and to better directed and more efficient efforts toward prevention. The crusade against tuberculosis is truly a battle of the people, by the people, and for the people. It is not a doctors' fight merely, but all the forces of society—economic, social, moral, legislative, administrative, philanthropic—must be enlisted in this contest.

The benefits to the community which result from success in the prevention of disease extend, as a rule, far beyond the mere control of the particular disease in question, incalculable as this benefit may be. As regards tuberculosis, it has become increasingly apparent that successful prevention will be attended by improved conditions of living, of work, and of play; in a word, by a general social betterment of the people. It is this aspect

of the crusade which has very properly stimulated the interest of philanthropists, social workers, and statesmen.

When we contemplate the popular interest and enthusiasm which have already been aroused in the campaign against tuberculosis, the readiness to institute preventive measures, the large pecuniary resources which are available, and the great expenditure of money and of energy already made or in process of making, we must be impressed with the importance of making sure that our measures of prevention are really based upon accurate and full knowledge of the mode of spread of the disease, and are so applied as to yield the best results, in the most economical way, most surely and most quickly. The campaign must rest upon a sound scientific basis, and must be conducted along correct scientific lines. This scientific foundation is supplied mainly by the knowledge furnished by investigation of the subjects represented in this first section of the Congress, namely, the pathology and bacteriology of tuberculosis. Other sections of the Congress may seem to be concerned more directly with the marshalling of the forces, with the conduct of the assault, with the stirring of the martial spirit, and the appeal to arms, but ours is the division which must supply the ammunition and the weapons and the strategy of the campaign.

While our existing knowledge of tuberculosis already furnishes the basis for vigorous and intelligent measures of prevention against tuberculosis, it must be conceded that there are many important open problems awaiting further investigation, and that there is still much diversity of opinion regarding points essential to the proper conduct of the campaign. We may confidently anticipate that the proceedings of this section will contribute something of value toward the elucidation of some of these problems and toward a closer agreement of authoritative opinion. They will be, I trust, a source of pleasure and of profit to all in attendance.

THE VIABILITY OF THE TUBERCLE BACILLUS.

By M. J. Rosenau, M.D.,
Director Hygienic Laboratory, U. S. Public Health and Marine Hospital Service, Washington, D. C.

All observers agree with Koch that human sputum is the main source of human tuberculosis; whether the bacillus is oftenest inhaled or swallowed, whether most frequently taken into the body dried or moist, are questions still at issue. The viability of the tubercle bacillus in sputum, therefore, assumes a special significance in connection with questions concerning the channels of infection and methods of transmission. A correct understanding of the viability of the tubercle bacillus is also of vital importance so far as prophylactic measures are concerned.

No one questions that many of the tubercle bacilli are still alive and virulent in the droplets that are sprayed from the mouths of consumptive persons. Likewise, many of the bacilli must be fresh and active when deposited by consumptives upon drinking-cups, spoons, towels, or other articles, mouthed by well persons shortly afterward, and without intervening cleansing. Whether the bacilli remain alive and virulent in dried and pulverized sputum to such an extent as to frequently form a dangerous part of the dust of rooms and streets is a question still open for solution.

Two principal destructive agencies act on the tubercle bacillus in sputum expectorated on streets, floors, and other places: (1) Desiccation, and (2) the action of light. The bacillus also has to contend against other destructive agencies, such as the influence of putrefaction, etc.

The Tubercle Bacillus and Its Supposed Spore.

Koch at first believed that the tubercle bacillus contained spores. He was led into this error by the beaded appearance of the rod. We now know that the tubercle bacillus does not possess the resistance characteristic of endogenous spores, such as the spore of the anthrax bacillus, the tetanus bacillus, and the hay bacillus.

Two circumstances led early investigators into wrong conclusions as to the viability of the tubercle bacillus. One was the belief that the organism contained spores. The other was ignorance of the rôle played by dead tubercle bacilli. Some of the earlier workers spent much time in trying to

differentiate the resistance of the tubercle bacillus with and without spores. These earlier results are still quoted, without qualification, in most of the recent text-books and writings upon the subject. The notion that the tubercle bacillus has a spore is not altogether dead, and has created an exaggerated idea of its hardiness and resistance.

The Tubercle Bacillus and Its Waxy Substance.

It was soon found that, although the tubercle bacillus does not have a true spore, it contains an unusually large quantity of waxy substance, fats, and fatty acids.* It is supposed that these fatty substances surround the rod, thus affording it a protecting covering. This envelop is supposed to hinder drying, and also to protect the bacillus against the direct injurious influences of various external agencies.

The presence of the unusual amount of fatty and waxy substances led to a revision of our views upon the subject of the viability of the bacillus by placing it in an isolated and intermediate position between the spore-bearing and the non-spore-bearing rods. As to just how far this view is justified will be discussed subsequently.

Acid-fast Property.

The difficulty with which the tubercle bacillus takes the basic aniline dyes, and the great tenacity with which it holds them, are noteworthy. True spores also stain with difficulty and resist the decolorizing action of acids. The analogy between the staining and decolorizing property of spores and of the tubercle bacillus is not infrequently mentioned in the literature as indicating far greater resistance on the part of the tubercle bacillus to heat, dryness, putrefaction, chemicals, etc., than is the case with the great run of non-spore-bearing organisms. Except for the analogy, there is no indication that there is a definite relation between the viability of an organism and the ease or difficulty with which it stains and decolorizes. In fact, some protozoa, certain spirochetes, and other frail microörganisms stain with more or less difficulty or require special technic.

The True Position of the Tubercle Bacillus.

Some of the more recent work upon the viability of the tubercle bacillus indicates that it may show little, if any, greater resistance to heat, dryness,

* According to Hammerschlag, 26.2 per cent.; 22 per cent., Klebs; 37 per cent., de Schweinitz and Dorset; 20 to 25 per cent., Koch and Aronson; from 8 and 10 to 25 and 26 per cent., Ruppel, of alcohol-ether extract. This consists of fatty acids and neutral fat and a waxy substance. In contrast to the tubercle bacillus, other bacteria contain only 1.7 to 7 and 10.1 per cent. alcohol-ether extractives. According to Aronson, the tubercle wax is, for the most part, not in the bacillus, but between the bacilli as a product of secretion.

putrefaction, chemicals, sunlight, and other injurious agencies than the great bulk of non-spore-bearing bacteria. Its usual habitat in albuminous, mucoid, or fatty substances, such as pus, mucopus, necrotic material, milk, etc., protects it to a certain extent. This protection, however, is an accident of its environment rather than an inherent vital property.

We now know that 60° C. for twenty minutes is sufficient to kill the tubercle bacillus in milk, bouillon, water, and other fluids.* At one time it was believed that the tubercle bacillus resisted boiling temperatures. Experiments have resulted in gradually reducing the accepted thermal death-point until now we can state, with considerable confidence, that the tubercle bacillus is very little, if any, more resistant than a number of other non-spore-bearing bacteria, for instance, the typhoid bacillus, the dysentery bacillus, and the colon bacillus.

Some writers seem to consider it rather remarkable that the tubercle bacillus—an organism without a spore—should live several months in dust, in water, on fabrics, in sputum, etc. For instance, Schill and Fischer found it alive one hundred and eighty-six days in dried sputum; Toma, virulent up to ten months; Sawizky, dead after two and a half months; Twitchell found it virulent on a handkerchief seventy days, but dead in one hundred and ten days; Rickards, Slack, and Arms found it virulent after eighty-five days, kept dark and dry; and Feltz found dried sputum, in a room, virulent up to seven and nine months.

It is possible, however, to cite from the literature, instances of other non-spore bearing organisms living similar periods of time under like conditions. For instance, observers have found that the cholera spirillum may live for one hundred and fifty to two hundred days when dried under favorable conditions. Sirena and Alessi report that such a frail organism as the Diplococcus pneumoniæ did not die until after one hundred and ninety-two days when dried on silk threads and kept in a moist room, and one hundred and sixty-four days in a dry room. In some experiments on the plague bacillus I found it to live over four months on a piece of dry sponge, and over three months in water.† Similar instances might be multiplied.

On the other hand, the following instances are given of experimenters who report a relatively short vitality for the tubercle bacillus dried in sputum not exposed to direct sunlight: Cadéac found it dead in ten days and sometimes less; Hill, sixteen days; Ransom and Delepine, nineteen days; and Galtier, after thirty days.

The question at issue, from a practical standpoint, is, not how long the

* Rosenau, M. J.: "The Thermal Death-points of Pathogenic Microörganisms in Milk," Hyg. Lab. Bull. No. 42, U. S. Pub. Health and Mar. Hosp. Serv., Washington, 1908.

† Rosenau, M. J.: "Viability of the Bacillus pestis," Hyg. Lab. Bull. No. 4, U. S. Mar. Hosp. Serv., Washington, 1901.

tubercle bacillus may *occasionally* survive in dried sputum, but how soon it *usually* dies or becomes harmless. In order to determine this point much more data will be required than are now available.

All authorities who have worked upon the subject seem agreed that the tubercle bacillus loses its virulence before it finally dies. This is also the case with other pathogenic non-spore-bearing bacteria.

It seems that the more carefully the tubercle bacillus is studied, the nearer its viability is seen to approach that of other bacteria of its class.

Criterion of Death.

It is difficult to determine just when a microörganism dies. This difficulty is increased in the case of the tubercle bacillus. The reluctance with which this organism grows upon artificial media makes cultural methods totally inapplicable; it is necessary to resort to animal inoculations. Here again we meet an unusual difficulty, for the dead tubercle bacillus may produce lesions indistinguishable from those which are caused by live cultures.

A study of the literature shows that much of the work upon the viability of the tubercle bacillus has little value, for lack of a clear criterion of death. Many experiments will be found recorded in which the tubercle bacillus is exposed to various influences, such as drying, heat, chemicals, sunlight, putrefaction, etc., and after a certain period of time the dried material is inoculated into rabbits or guinea-pigs. In about two months after the inoculation the animal is usually killed, and if caseous abscesses and other lesions about the site of inoculation are found, and the tubercle bacillus is rediscovered in stained smears made from the local lesions, the conclusion is drawn that the tubercle bacillus is alive, and the results are recorded as positive.

It is now well known that the dead tubercle bacilli may cause lesions characterized by giant-cells, caseous necroses, etc. I have found that moderately large amounts of tubercle cultures surely killed by heat (100° for an hour), when injected into the peritoneal cavities of guinea-pigs, may cause very extensive lesions. So closely do these lesions sometimes resemble those produced by the living bacteria that, unless the portions of the spleen, liver, lungs, glands, and local processes are inoculated into another animal, it is not possible to know whether we are dealing with the effects of living or of dead bacteria. When the lesions are plainly generalized throughout the *substance*, of the liver, spleen, lungs, etc., these secondary inoculations may not be necessary.

The various organs (whether they contain macroscopic lesions or not), bits of tissue, and parts of lesions, should be ground up with salt solution and the extract injected into the peritoneal cavity of a normal (secondary) guinea-pig; if the bacteria are alive, there will develop a generalized fatal

tuberculosis; if dead, only a trifling localized process. This method is time-consuming and expensive, but is often indispensable as a final test.

It is well known that tuberculin cannot distinguish the lesions produced by live tubercle bacilli from those produced by dead ones. In a series of experiments on this point, I found that three out of eight guinea-pigs, with lesions produced by dead tubercle bacilli, died as a result of a subcutaneous injection of 2 c.c. of tuberculin (O. T.).*

An Explanation of Discrepancies in Published Reports.

When one reads the literature upon the subject of the viability of the tubercle bacillus, he is struck first by the extravagant claims made by some investigators for the prolonged life and unusual resistance of the tubercle bacillus. There are also marked discrepancies in the results obtained by different experimenters with apparently well-planned and carefully controlled work.

It seems that one of the main reasons for these variations is the failure to take note of the pathogenic power of the dead tubercle bacillus. In 1884 Schill and Fischer studied the action of a temperature of 100° C. upon tuberculous sputum. They reported that 100° C. of dry heat did not surely destroy the virulence of tuberculous sputum, whether dry or moist. These experiments are frequently quoted to show that the tubercle bacillus resists boiling temperatures; but we now know that the thermal death-point of the tubercle bacillus is considerably less than that indicated by earlier work.

Schill and Fischer also found that the bacillus retained life in sputum dried one hundred and forty-three days, but was not infective after one hundred and seventy-nine days. The method used consisted in inoculating guinea-pigs, but the authors do not give the details of the experiments.

In view of the fact that earlier investigators fell into error concerning the thermal death-point of the tubercle bacillus, it may be assumed that a repetition of their work upon the viability of the organism when dried in sputum, etc., may cause us to revise our views upon the subject.

According to the work of Kitasato, most of the tubercle bacilli in sputum, in cavities, and even in the tissues are dead. This opinion was based largely upon negative results obtained by cultural methods. As our present cultural methods do not give trustworthy evidence upon the viability of the tubercle bacillus, further work upon the subject is necessary, especially as Straus confirmed the inadequacies of such methods, particularly in obtaining first cultures of tubercle bacilli. A certain acclimatization is necessary for their ready growth upon artificial media. It is true that Kitasato claims

* Rosenau, M. J.: "The Thermal Death-points of Pathogenic Microörganisms in Milk," Hyg. Lab. Bull. No. 42, U. S. Pub. Health and Mar. Hosp. Serv., Washington, 1908.

to have seen, in some cases, successful inoculation into guinea-pigs; but Straus has made analogous experiments with opposite results.

The Short Life of Cultures Contrasted with the Long Life under Unfavorable Conditions.

The comparatively short life of pure cultures of the tubercle bacillus, under most favorable conditions, contrasts strangely with the long life claimed for the organism under unfavorable conditions. It appears that the life of the tubercle bacillus in cultures is shorter the more rapid and luxuriant the growth.

Cornet states that serum cultures remain alive about six months; glycerin-agar cultures are often partially or wholly dead in six to eight weeks. It appears that cultures of avian tubercle retain their vegetability and pathogenic power much longer—according to Maffucci, even two years. Straus states that cultures of human tubercle are only exceptionally capable of reproduction after five to six months; after eight to twelve months they fail regularly. The virulence of the cultures likewise diminishes with age. According to Theobald Smith, tubercle cultures are usually dead after three months.

The Thermal Death-point.

In a recent publication* I reported the results of my experiments upon the thermal death-points of pathogenic microörganisms in milk. Nine experiments were made with five different cultures of the bovine tubercle bacillus. The conclusion was drawn that the tubercle bacillus in milk loses its infective properties for guinea-pigs when heated to 60° C. and maintained at that temperature for twenty minutes, or to 65° C. for a much shorter time.

It should be remembered that the milk in these tests was very heavily infected with virulent cultures, as indicated by the prompt death of the control animals. Milk would practically never contain such an enormous amount of infection, under natural conditions. It is justifiable to assume that, if 60° C. for twenty minutes is sufficient to destroy the infectiveness of such milk when injected into the peritoneal cavity of a guinea-pig, any ordinary market milk, after such treatment, would be quite safe for human use by the mouth, so far as tubercle bacilli are concerned.

It is difficult, if not impossible, to summarize the work of others upon the thermal death-point of the tubercle bacillus. The following table necessarily leaves out many factors:

* *Loc. cit.* A complete review of the literature upon the subject will be found upon pp. 34–47.

SHOWING THE THERMAL DEATH-POINT OF THE TUBERCLE BACILLUS AS FOUND BY VARIOUS INVESTIGATORS.

Investigator.	Killed at—	Not Killed at—
Martin, 1882	....	80°.
May, 1883	By cooking.	
Sormani, 1884	Boiling, 5 minutes.	90° for 10 minutes.
Schill and Fisher, 1884	....	100°.
Voelsch, 1887	....	100°, boiling twice.
Yersin, 1888	60°, 10 minutes (—spores). 60°, 10 minutes (+spores).	
Bitter, 1890	68°, 20 minutes.	
Bang, 1891	70°, 5 minutes (enfeebles). 60°, 5 minutes (sometimes enfeebles). 80°, (sometimes kills). 85°, (always kills).	
Bonhoff, 1892	60°, 20 minutes.	50°, 60 minutes.
Grancher and Ledeux-Lebard, 1892	60°, 5 minutes (attenuates). 70°, 1 minute (kills).	
Forster, 1892	60°, 6 hours. 95°, momentary.	55°, 3 hours. 60°, 45 minutes. 80°, momentary.
De Man, 1893	55°, 4 hours. 60°, 1 hour.	60°, 45 minutes.
Schroeder, 1894	60°, 15 minutes.	
Woodhead, 1895	50°, 15 hours. 60°, 8 hours. 60°, 45 minutes. 70°, 45 minutes. 70°, 2½ minutes.	90° (results contradictory).
Marshall, 1899	68°, 20 minutes.	60°, 10 minutes.
Th. Smith, 1899	60°, 15 to 20 minutes.	
Morgenroth, 1900	55°, 3 hours.	70°, 10 minutes. 100°, momentary.
Kobrak, 1900	50°, 4 hours.	
Beek, 1900	100°, 3 hours.	100° 80°, 30 minutes.
Galtier, 1900	....	85°, 6 minutes.
Russell and Hastings, 1900	60°, 20 minutes.	
Herr, 1901	65°, 15 minutes.	80°, 5 seconds.
Hesse, 1901	60°, 20 minutes.	
Levy and Burns, 1901	65°, 15 minutes.	
Barthel and Stenström, 1901	....	70°, 15 minutes.
Bang, 1902	....	60°, 15 minutes.
Tjaden, 1903	85°, 1 to 2 minutes.	
Rullmann, 1903	65°, 30 minutes.	60°, 20 minutes.
Barthel and Stenström, 1904	80°, 1 minute (uncoagulated).	80°, 1 minute (coagulated).
Russell and Hastings, 1904	71°, 1 minute.	
Zelenski, 1906	....	76°, 20 minutes.
Rosenau, 1907	60°, 20 minutes.	

The above tabular statement shows that my results agree with the work of Yersin, Bonhoff, Schroeder, Th. Smith, Russell and Hastings, and Hesse, in that 60° for twenty minutes and less is sufficient to kill the tubercle bacillus.

I am now conducting a further series of experiments upon the thermal

death-point of the tubercle bacillus in butter and milk, naturally and artificially infected, and, while this work is not yet completed, the indications again are that 60° for twenty minutes is quite sufficient to kill the organism.

Viability in Dried Sputum.

There seems to be a general agreement that the tubercle bacillus may remain alive and virulent in dried sputum for several months. Stone's unusual figure of three years does not stand the light of criticism. The main point established, however, is that the tubercle bacillus may survive in sputum after it dries and is reduced to dust, so that its inhalation may be a danger; how much of a danger, depends upon other questions not yet solved.

It is well known that when non-spore-bearing bacteria are dried, all but a few soon perish; but these few sometimes survive for unusually long periods of time. This rule probably holds in the case of the tubercle bacillus, for, unfortunately, we have no quantitative method of determining the number of tubercle bacilli remaining alive. The survival of a few bacilli which are virulent for experimental animals when injected in enormous quantities (as is usually done in laboratory work) would not necessarily mean very grave danger to human beings under natural conditions of such material in dust, especially when exposed to the sun, etc.

The following is a tabular abstract of the literature upon the viability of the tubercle bacillus dried in sputum:

DRIED TUBERCULOUS SPUTUM UNDER DIFFERENT CONDITIONS.

Author.	Conditions.	Not Killed.	Killed.
Villemin, 1869.....	Dried tuberculous sputum.	Several hours.	
Koch, 1882.....	Dried tuberculous sputum.	8 weeks.	
Malassez and Vignal, 1883.....	Alternate drying and moistening eight times of tuberculous sputum.	12 days.	
Schill and Fischer, 1884.....	Sputum containing tubercle bacilli with "spores" dried on glass plates.	126 days.	179 days.
	Same, with "spores."	186 days.	226 days.
De Thoma, 1886....	Dried tuberculous sputum.		10 months.
Sormani, 1886.....	Dried tuberculous sputum.	2 months.	Virulence decreases after 2 months.
	Same, on linen.	6 months.	Lost at end of 4 months.
Cadéac and Malet, 1888.....	Pieces dried tuberculous lung on paper exposed in laboratory.	43 days.	102 days.
	Dried tuberculous lung allowed to decompose in outer air.	76 days.	
	Dried tuberculous lung allowed to decompose in outer air.	80 days.	

DRIED TUBERCULOUS SPUTUM UNDER DIFFERENT CONDITIONS.—(*Continued.*)

AUTHOR.	CONDITIONS.	NOT KILLED.	KILLED.
Cadéac and Malet, 1888	Dried tuberculous lung allowed to decompose in outer air.	150 days.	After 150 days.
De Souza, 1889	Dried walls of cavities insufflated; caused tuberculosis in 12 of 14 guinea-pigs; time of drying not stated.		
Galtier, 1889	Dried tuberculous "material" exposed to air and light at 30° C.	38 days.	
	Same, at room temperature.	30 days.	After 30 days.
Feltz, 1890	Dried tuberculous sputum in road dust, exposed to weather.	Over 7 months.	
	Same, exposed to sun.	About 140 days.	
	Dried sputum in rooms.	7 to 9 months.	
Sawizky, 1891	Tuberculous sputum dried under ordinary conditions of living-room.	2½ months.	
Stone, 1891	Dried tuberculous sputum.	3 years.	
Ransome and Delepine, 1894	Tuberculous sputum exposed in watch-glasses to—		
	(*a*) Air and light 4 days, then 15 days in the dark.	19 days.	
	(*b*) Air and darkness 8 days, then 11 days in darkness.		19 days.
	(*c*) Close cupboard 19 days.	19 days.	
Hill, 1903	Tuberculous sputum exposed on glass rods in drying box to diffused daylight and slow diffusion of air.		16 days.
Cardéac, 1905	Tuberculous sputum spread on glass, exposed to air and light.	2 days.	4 days.
		4 days.	6 days.
		6 days.	10 days.
	Tuberculous sputum in thick layers dried on marble slab.		14 days.
Twitchell, 1905	Tuberculous sputum in paraffined bottles, in dark moist box	Produced lesions: at end of 170 days.	No lesion after 188 days.
	Tuberculous sputum in paraffined bottles in dark closet.	160 days.	188 days.
	Tuberculous sputum in paraffined bottles, in diffused light.	124 days.	175 days.
	Tuberculous sputum in paraffined bottles, in thermostat.	33 days.	100 days.
	Cotton-stoppered bottles, in dark, moist box.	157 days.	172 days.
	Cotton-stoppered bottles, in dark closet.	100 days.	141 days.
	On ice.	102 days.	153 days.
	On handkerchief.	70 days.	110 days.
	On towel.	70 days.	110 days.
	On carpet.	39 days.	70 days.
	In sand, in moist light place.	123 days.	148 days.
	In sand, in dry light place.	30 days.	70 days.
	Open bottles, outdoors, winter.	110 days.	132 days.
Sormani, 1906	Dried tuberculous excretion at 35° C.	15 days.	

DRIED TUBERCULOUS SPUTUM UNDER DIFFERENT CONDITIONS.—(*Continued.*)

AUTHOR.	CONDITIONS.	NOT KILLED.	KILLED.
Rickards, Slack, and Arms, 1908	Dried tuberculous sputum in tenement-house:		
	(*a*) Sunlight and dry.	Experiments under way.	
	(*b*) Diffused light and dry.	1 month.	
	(*c*) Dark and dry.	85 days.	
	(*d*) Dark and damp basement.	Experiments under way.	

THE EFFECT OF SUNLIGHT.

Koch's dictum, that direct sunlight kills the tubercle bacillus within a few minutes to several hours, has been confirmed by all workers except Feltz. The time required depends upon the brightness of the ray, the time of the year, the latitude, the temperature, the thickness and opacity of the layers, the medium in which the bacilli are embedded, and other conditions.

This action of light corresponds to the well-known germicidal power of the ultra-violet rays of the spectrum upon other non-spore-bearing bacteria, and must play an important rôle in diminishing the danger from tuberculous sputum and dust out-of-doors.

The following table gives the data in brief upon the subject:

EFFECT OF DIRECT SUNLIGHT UPON THE TUBERCLE BACILLUS.

AUTHOR.	CONDITIONS.	NOT KILLED.	KILLED.
Koch, 1890	Tubercle bacilli.		Few minutes to several hours.
Feltz, 1890	Tuberculous sputum in road dust exposed to sun.	About 140 days.	
Ransome and Delepine, 1894	Pure culture dried on paper in thin layers.		12¼ hours.
Migneco, 1895	Tuberculous sputum on linen and woolen cloth.		24 to 30 hours. Virulence diminishes in 10 to 15 hours.
Gardiner, 1898	Tuberculous sputum on		
	Sand,	1¾ hours.	
	Stone,	2 hours, 5 minutes.	
	Wood,	24 hours (localized tuberculosis).	
Mitchell and Crouch, 1900	Tuberculous sputum placed upon sterilized soil.	35 hours. (Virulence diminished after 20 hours.)	45 hours.
Jousset, 1900	Tuberculous sputum, exposed to dust and sunlight.		4 hours.
Annett, 1903	Dried mucopurulent sputum in small masses about size of one expectoration.	2 to 24 hours.	48 hours.

EFFECT OF DIRECT SUNLIGHT UPON THE TUBERCLE BACILLUS.—(*Continued.*)

AUTHOR.	CONDITIONS.	NOT KILLED.	KILLED.
Cadéac, 1905.....	Tuberculous sputum on a board.		24 hours.
	Tuberculous sputum in glass plates exposed to artificial light.	24 hours.	48 hours.
Twitchell, 1905	Tuberculous sputum exposed to direct sun-rays.	1 hour.	7 hours.
Di Donna, 1907	Pure cultures.	6 days.	8 days.
Koch, 1890.....	Cultures of tubercle bacilli exposed to dispersed daylight near window.		5 to 7 days.
Ransome and Delepine, 1894	Pure cultures dried on paper in thin layers, exposed to air and light.		4 days.
	Same, exposed to sunlight.		12¼ hours.

THE TUBERCLE BACILLUS IN WATER.

The tubercle bacillus may probably live and remain virulent in water for several months. We have indications of this in the work of Straus and Dubarry (1899); Muschold (1900); Galtier (1889); Chantemesse and Widal (1888); and Cadéac and Malet (1888).

Since the danger of ingesting the tubercle bacillus is now well established, its presence in drinking-water assumes a special significance. Tuberculous cattle, as well as tuberculous individuals, swallow and discharge large numbers of tubercle bacilli in their dejecta. Sewage polluted water used for drinking purposes may, therefore, harbor dangers other than the intestinal order of diseases, such as typhoid, cholera, etc. Dixon found acid-fast organisms resembling the tubercle bacillus morphologically in the sewage from hospitals in Philadelphia. Sedgwick and MacNutt* (1908) have examined the theory, first enunciated by Hiram F. Mills and others, but first definitely formulated and published by Allen Hazen, that "for every death from typhoid fever avoided by the purification of public water-supplies, two or three deaths are avoided from other causes." Sedgwick and MacNutt studied the influence of the purification of polluted water-supplies in Lowell and Lawrence, Mass., compared with similar data for Manchester, N. H. The theorem was proved true, not only for the cities mentioned, but also for certain other cities, including Hamburg, Germany. Among the causes other than typhoid fever for which the death-rates are diminished, *pulmonary tuberculosis*, pneumonia, and infant mortality are prominent. The occurrence and the viability of the tubercle bacillus in water, therefore, become a fertile field for research.

The following is a brief abstract of the work done to date upon the subject:

* Sedgwick, W. T., and MacNutt, Scott: "Typhoid Fever and the Purification of Public Water Supplies," Science, vol. xxvii, August 14, 1908, p. 215.

TUBERCLE BACILLUS IN WATER—PUTREFACTION AND MISCELLANEOUS CONDITIONS.

Author.	Conditions.	Not Killed.	Killed.
Sormani, 1886.....	Tubercle bacillus in water.	12 months attenuated, but not killed.	
Straus and DuBarry, 1899.....	Tubercle cultures in water of the river Oureq; at 20° C.,	27 days	
	38° C.,	95 days.	
	35° C.,	30 days.	
	Tubercle cultures in distilled water;.....30° C.,	24 days.	
	38° C.,	115 days.	
	35° C.,	25 days.	
Galtier, 1889.....	Tuberculous spleen in water, 3° to 8° C.,	17 days.	
	Tuberculous products of pigs and cows in running and stagnant water; 17°, 13°, 0° C.	14 days.	
	Tuberculous products of cow in running water, 4° to 10° C.	2 months.	
Muschold, 1900.....	Tuberculous sputum in water, sewage, etc.	A number of months.	
	In sewage-polluted water.	6 months.	
Cadéac and Malet, 1888.....	Tuberculous lung, buried.	77 days.	
		124 days.	
		159 days.	
		167 days.	Results negative after 167 days.
	Fragment of tuberculous lung in running water.	25 days.	
	Piece of tuberculous lung in bowl of water exposed on outer window-sill.	76 days.	
	Piece of tuberculous lung in bowl of water exposed on outer window-sill.	120 days.	150 days.
	Tuberculous lung titrated with water, exposed to air in bowl.	16 days.	67 days.
Lösener.....	Tuberculous organs placed in cadavers of hogs and buried.	3 months.	4 months.
Hance, 1898.....	Tuberculous sputum, kept fluid in well-corked bottle.		17 months.
Kirstein, 1905.....	Dust from papers and books infected with fine spray containing tubercle bacilli.	8 days.	4 months.
	Sputum dust.	4 days.	7 months.
	Cloth fibers containing tubercle bacilli.	5 days.	10 months.
	Street dust containing tubercle bacilli.	3 days.	8 months.
Petri, 1890.....	Portions of exhumed human bodies.	3 months.	
Schotellius, 1890....	Buried phthisical lungs.	Several years.	

Literature.

The following is an abstract of the published work bearing on this subject. Some of these articles now have little more than historical value. Others are fragmentary, or report the results of a single or a few inoculations. In many of the articles important details of the experiments are omitted, so that it is not possible to form a just valuation of their worth.

The literature upon the thermal death-point of the tubercle bacillus was fully abstracted in Hygienic Laboratory Bulletin No. 42, and is therefore not repeated here.

Annett* collected expectorations from the streets of London during the winter months by means of sterilized swabs, which he placed in sterilized test-tubes. Portions of each were inoculated subcutaneously in two guinea-pigs. The animals were kept under observation during the subsequent eight weeks or more. Other portions were used to make two smears from each on glass slides which, after being stained by the Ziehl-Neelsen method, were examined under a $\frac{1}{12}$ oil-immersion objective. Mucous, mucopurulent, and purulent accumulations were taken indiscriminately, only the more liquid expectorations being neglected. One hundred and eight such expectorations were examined. Neglecting those cases which resulted in the death of both experimental animals within a few days, out of 105 specimens of sputum collected, five were proved to contain virulent tubercle bacilli, a percentage of 4.76, three of the five being demonstrated microscopically. Some of the collections certainly were nasal secretions, discharged by way of either the anterior or posterior nares.

Annett† (1903), after reviewing the work of preceding authors upon the action of sunlight on tuberculous sputum, states that their results appear to be somewhat at variance. He conducted a few experiments with the object in view of determining the effect of the English climate upon the tubercle bacillus.

A quantity of mucopurulent sputum from a case of pulmonary tuberculosis, which showed a number of tubercle bacilli in every field, was divided into small masses of the size that would be ordinarily expectorated by a person on the street. These were exposed to the action of sunlight for varying periods of two, four, six, eight, twelve, twenty-four, and forty-eight hours, on four days having an average temperature of about 65° F. and a light breeze.

Twenty-four hours of exposure to sunlight, during eight of which there was direct sunlight, throughout the remainder the sun being slightly

* Annett, H. E.: "Tubercular Expectoration in Public Thoroughfares: an Experimental Inquiry," Thompson Yates Lab. Reports, vol. iv, pt. 2, 1902, p. 359.

† Annett: "Tubercular Expectoration in Public Thoroughfares," Jour. State Med., London, vol. xi, 1903, pp. 462–466.

clouded, failed to kill the tubercle bacilli, as shown by inoculation into guinea-pigs. All the specimens exposed for two to twenty-four hours contained virulent bacilli. Forty-eight hours' similar exposure, however, killed the bacilli.

Baldwin* (1907) says that dry bacilli from cultures may lose virulence in three weeks, but the more important question as to their viability in naturally dried sputum involves such varying conditions that the preservation of infective power depends upon the size and thickness of the sputum mass, its quality, its place of deposit with reference to the character of the surface, and, most important of all, its exposure to light, heat, and air. When sputum of tenacious character is dried in large masses, the bacilli are shut out from the air in the hard, glue-like crusts; and in a dark, cool place, such as a basement room or the corridor of many city dwellings, the maximum period of vitality may be assumed to be from six to eight months; this is the estimated limit given by Cornet.

Putrefaction.—Putrefaction of sputum and tuberculous animal tissues usually destroys the tubercle bacilli within a few days (Baumgarten and Falk, de Thoma, Schill and Fischer). It is dependent upon the nature of the process, and how rapidly it takes place, whether the products of decomposition are harmful to the bacilli or not. Galtier was able to infect animals after twelve months with putrid spleen and lung. This question is of interest in relation to the persistence of virulence in the diseased cadavers and excreta of man and animals, because of the possible danger of transmission by means of infected earth, insects, etc. Cadéac and Malet found buried tuberculous lungs virulent after five months, but Klein not after six weeks. Gärtner concluded that tubercle bacilli could survive months in feces. Lortet and Despeignes showed that earthworms could harbor the bacilli when in contact with the sputum, but decomposition ordinarily must obviate danger from such sources.

Cadéac † (1905) made the following observations:

1. *Rôle of Powdered Tuberculous Matter.*—To determine that pulmonary tuberculosis results from the introduction of infected powdered material into the respiratory tract, and to confirm the value of this method of contagion, the following conditions under which desiccation takes place should be examined:

(1) Light; (2) darkness. To determine with what they come in contact when they fall—upon absorbent matter (floors, shelves, carpets); upon non-absorbents (varnished wood, glass). To examine under what conditions the sputum was converted into dust. To determine the degree of virulence

* Baldwin: "Tuberculosis: History and Etiology," Osler's Modern Med., vol. iii, 1907, p. 156.

† Cadéac: "Sur la contagion de la tuberculose," Rev. d'hyg., Par., vol. xxvii, 1905, pp. 961–980

at the time the conversion is effected. To collect this dust and cause its inhalation to determine its infectivity by the respiratory tract.

Desiccation of Sputum.—This is effected slowly. It is necessary to determine the time required for this conversion, taking into account the character of the surfaces upon which the sputum is exposed to natural light, artificial light, and to darkness.

1. *Desiccation under Natural Light.*—Tuberculous sputum is placed upon glass, upon the floor, on the hearth, and mixed with the ashes.

(*a*) Spread in large quantity upon a plate of glass, the sputum adheres strongly in drying; it covers the glass, and the glue which it forms shows no tendency to detachment for conversion into dust. At room temperature it requires ten to twelve days to be easily detached and reduced to powder.

What becomes of the virulence during this transformation?

Particles of sputum are taken from time to time and inoculated subcutaneously and intraperitoneally into guinea-pigs, to determine the virulence. This inoculation is difficult, because the dried sputum takes its viscosity from that which is moist.

At the end of two days' exposure to air and light the virulence is intact; two guinea-pigs were inoculated on February 17th: one died on May 30th; the other May 10th, of generalized tuberculosis of liver, spleen, and lungs; the glands in the vicinity of the site of inoculation are hypertrophied and caseous. At the end of four days, of the two guinea-pigs inoculated, the result is positive for one; negative for the other.

At the end of six days, of the two guinea-pigs inoculated with the thicker part of the sputum layer, the result was positive for one; negative for the other, but the lesions were extremely discrete, and consisted of a few granulations, on the spleen and two in the lungs.

At the end of ten days two guinea-pigs were inoculated intraperitoneally with the powder collected, suspended in distilled water, and filtered, with a result that permits the supposition that they were not virulent. This determination is not absolutely exact; at the time when these particles of dust were inoculated with a negative result a larger part were collected, and very finely pulverized and insufflated under a bell-jar containing four guinea-pigs; one of the guinea-pigs, in addition to inhaling the dust, ate the powder collected in considerable quantity on the glass floor.

Notwithstanding, three of the four guinea-pigs remained perfectly healthy for three months; the fourth, that had inhaled and eaten the powder, presented at autopsy the characteristic symptoms of ingestion tuberculosis: tuberculous granulations of the palate, ulcer of the tongue, hypertrophy and caseation of the maxillary and retropharyngeal glands, which were as large as hazel-nuts, two tuberculous granulations in the lungs, spleen peppered with granulations; other viscera exempt. Here ingestion and inhalation

combined produced a generalized infection, which inoculation failed to induce.

(*b*) The destruction of virulence in the sputum is more or less rapid, according to the intensity of the light and the thickness of the layer of sputum; sputum placed in thick layers on plates of marble and placed on the drying stove for fourteen days, and inoculated on the internal surface of the thigh of three guinea-pigs, produced no lesion.

(*c*) Sputum placed on the floor, not waxed, but porous, is dried much more rapidly, with the result that it can be readily reduced to powder.

A large quantity of sputum was placed on a board and exposed on June 21st to the direct light and heat of the sun. Particles of the sputum were inoculated at the end of twenty-four hours, forty-eight hours, and seventy-two hours, on the internal surface of the thigh of two guinea-pigs for each series; these animals, sacrificed on August 10th, were found to be perfectly healthy.

(*d*) Sputum mixed with ashes forms a very sticky mass, later it becomes solid, too large to be lifted by the air, too thick to be penetrated by light, of such kind that its desiccation has the greater chance of being accomplished without destruction of the bacilli. This mixture is under the analogous conditions of sputum dried in the dark; its virulence is similarly preserved; inoculated, after having been suspended in water and filtered, it can produce tuberculosis.

2. *Desiccation under Artificial Light.*—Artificial light, such as gas and electricity, rapidly destroys the virulence of sputum spread upon plates of glass placed at a distance of one meter from these sources of light. Sputum, thus exposed for twenty, ten, six, or four days, or only forty-eight hours in thin layers, when inoculated into guinea-pigs, has given negative results. Only sputum thus exposed for twenty-four hours can communicate the disease by inoculation. But such sputum is not sufficiently dried to be easily triturated and converted into powder capable of being inhaled.

3. *Desiccation in the Darkness.*—Powdered sputum, dried at normal temperature, or in an incubator at 36° C., preserves its virulence uncertainly, *i. e.*, inoculation of such desiccated sputum gives uncertain results. While inoculation of such sputum may give negative results, its ingestion will be positive. It appears that the bacilli are incorporated in a viscous stratum of sputum, imprisoned, so that they cannot vegetate, and inoculation remains ineffective. Many times the author has found that inoculation beneath the skin of guinea-pigs of such sputum powder failed to produce tuberculosis.

Positive results with such dried sputum are obtained only after a long time; the development of tuberculosis, resulting from the subcutaneous inoculation of this so dried sputum, triturated and suspended in a small quantity of distilled water and filtered, is extremely slow. Many of the animals inoculated in March have lived until August 10th, and may live longer.

At autopsy they show tubercular lesions upon the spleen, the lung, with a small focus of induration at the site of inoculation.

Thus, sputum distributed in dwellings or on discarded clothing, or stamped about, constitutes a sticky product, which solidifies slowly, and is pulverized with difficulty after a long time. While this transformation is occurring, light is attenuating or destroying the virulence.

Once only were Cadéac and Malet able to obtain this transmission, and they thus contributed to the belief that contamination by the dust of rooms occupied by phthisics should be regarded as an accident.

The frequency of this accident can vary with the degree of cleanliness, of aëration, of aggregation of phthisical subjects, or with the exiguity of the rooms which they inhabit, and with the hygienic measures taken for the prevention of the accumulation in these places of sputum and dust.

It is necessary to multiply the experiments with the view of determining, as exactly as possible, though of necessity only approximately, the dangers of infection by the atmosphere of hospitals, public places, or the interior of houses. It is necessary to collect the dust of all these places and to cause its inhalation by animals. Heretofore, experiments have not been made under this procedure. The dust collected in hospitals, asylums, and apartments occupied by phthisics has always been inoculated either subcutaneously or intraperitoneally. Cornet succeeded in communicating tuberculosis to one-third of the animals inoculated. The results of his experiments are weakened either by the acid-resistant organisms or by an unknown cause.

Inoculations demonstrate its innocuity. When this virulence is not destroyed, the bacilli are incorporated, imprisoned in the desiccated stratum of the tuberculous sputum, vegetating very slowly, which permits of germicidal and phagocytic actions of the greatest intensity. The virulence is also very irregularly distributed in the mass of powder, and, generally, is little pronounced, as shown by the results of inoculation of sputum dried in the dark. It is, perhaps, the same when inhaled. To determine this point requires that these powdered sputa should be collected in places susceptible of being contaminated, and administered by inhalation for the purpose of determining their infectivity.

The researches made with the view of exposing these virulent powdered sputa are not numerous, it is, therefore, important to determine the degree of the infection of the atmosphere before going further.

The experiments of the author, relative to the resistance of the tubercle bacillus to desiccation, have demonstrated the destructive influence of air and light, especially in sputum. These experiments have shown that the presence of virulent bacilli in the air is rare.

In 1887 the author demonstrated that dust collected from the rooms occupied by phthisical patients only exceptionally produced tuberculosis by inoculation.

The author concludes that, notwithstanding all the favorable conditions for the infection of the experiment animals, it can be stated that it is very difficult to communicate tuberculosis by inhalation of dust prepared from dried tuberculous sputum.

Cadéac and Malet* (1888) submitted portions of tuberculous lungs, prepared in two different ways, to the influence of desiccation.

In the first, they placed small pieces of the lung of a tuberculous cow upon Joseph paper. When well dried by exposure in the laboratory, they were passed through a pepper-mill and the powder placed in flasks to be inoculated after a variable time into divers animals.

In the second experiment pieces of tuberculous lung, of the size of the hand, were placed in a soup bowl upon the window of the laboratory; in the beginning there was a slight putrefaction, then desiccation took place. The following results were obtained by inoculation under the two conditions:

1. *Powdered Tuberculous Matter.*—The powder was inoculated after forty-three days, one hundred and two days, one hundred and twenty-six days, and one hundred and fifty days of drying. After one hundred and two days, they were shown to be non-infective.

2. *Pieces of Lung Exposed to Desiccation in the Outer Air.*—After seventy-six days of desiccation, particles from the center of the piece of lung were inoculated into two rabbits, which rapidly developed tuberculosis.

Second Experiment.—Under similar conditions positive results were obtained after eighty days of desiccation.

In a *third experiment* the authors transmitted tuberculosis after one hundred and fifty days' exposure to the air. After this time the results were negative.

The authors have examined into the virulence of tuberculous lungs that have been submitted to putrefaction, developed as the result of burial, of running water, and of stagnant water, or of the exposure to the air of a tuberculous liquid.

3. *Burial of Tuberculous Lungs.*—On January 7, 1887, three pieces of tuberculous lung were buried.

First Experiment.—Two rabbits were inoculated after seventy-seven days' burial; results, positive. The bacilli were recovered according to Ehrlich's method in the putrefied products.

Second Experiment.—Inoculation after one hundred and twenty-four days in two animals; results positive.

Third Experiment.—Inoculation after one hundred and fifty-nine days in one animal; result positive.

Fourth Experiment.—Inoculation after one hundred and sixty-seven days in two animals; results positive.

* Cadéac and Malet: "Sur differents modes de transmission de la tuberculose," Cong. pour l'étude de la tuberculose, 1° sess., 1888, pp. 310–317.

After one hundred and sixty-seven days the animals died constantly of septicemia, so that it is impossible to determine if the tubercular virulence is definitely affected after this period of interment.

The results do not indicate any exceptional decrease in the power of resistance of tuberculous matter by putrefaction.

4. *Exposure of Tuberculous Lung in Running Water.*—A fragment of tuberculous lung was exposed to the action of a current of water (hydrant) for twenty-five days, when divers animals were inoculated, all of which became tuberculous. The inconvenience of this method of putrefaction has curtailed these experiments.

5. *Putrefaction of a Piece of Tuberculous Lung in a Bowl of Water, Placed on the Outer Window-sill.*—(*a*) Inoculation of two rabbits after seventy-six days; result positive.

(*b*) Inoculation of two rabbits after one hundred and twenty days; results positive.

(*c*) Inoculation of two rabbits after one hundred and twenty days; results negative.

One hundred and twenty days, then, is the limit of preservation of virulence of fragments of tuberculous lung under the conditions of humidity indicated.

As these experiments were made contemporaneously with those of burial, the following deduction is prompted.

Putrefaction in the open air affects the virulence of tuberculous matter more rapidly than interment. Is it the same when small particles of tuberculous matter are exposed under the form of small granulations in a large quantity of fluid? The following series of experiments were made to this end:

6. *Tuberculous Fluid Exposed to the Air and to Divers External Influences.*—A portion of a tuberculous lung was triturated and mixed with a large quantity of water. This virulent product was filtered and exposed to the air in a large bowl for sixteen days. It was successfully inoculated.

In the second series of experiments, undertaken March 5, 1887, with fluid prepared January 7, 1887 (sixty-seven days' exposure), a young pig was unsuccessfully inoculated.

Putrefaction has a more destructive effect when the fermentable tuberculous matter is exposed in smaller particles.

Chantemesse and Widal* (1888) made research as to the number of days the bacilli and "spores" of tuberculosis can remain viable in the water of the Seine.

Some of the specimens of water have been first sterilized and then inoculated with cultures of tubercle rich in spores; others were directly inoculated

* Chantemesse and Widal: "Resistance of the Tubercle Bacilli in River Water," Cong. pour l'étude de la tuberculose, 1° sess., 1888, p. 317.

after collection. A portion of the tubes of each group was kept in cold storage at a temperature of 8° and 12° C. Another portion was kept at room temperature between 15° and 20° C.

Every eight days a sample of the water that had been kept in the cold was inoculated into Pasteur flasks containing glycerin-bouillon, according to the method of Nocard and Roux; like inoculation was made of the water kept at room temperature; the flasks were then incubated. At the end of twenty days and a month, 1 c.c. of each tube, which without previous sterilization had been inoculated with tubercle bacilli, was inoculated intraperitoneally in guinea-pigs, with the following results:

Tubercle bacilli are alive fifty days in sterilized Seine water kept at 8° to 12° C. The same for seventy days, kept at 15° to 18° C.

In connection with the question of vitality of the tubercle bacilli is the more important question of their virulence. The second series of experiments was made to determine this point.

Guinea-pigs, inoculated intraperitoneally with 1 c.c. of the water, which contained tubercle bacilli after fifteen days, were killed at the end of two and a half months. None of them presented the least trace of tuberculosis. This result is due either to the small quantity of water inoculated, or to the attenuation of the bacilli in the relatively cold water.

With regard to the experiments upon the attenuation of the tubercle bacilli in water kept at ordinary temperature, the results are not invalidated by the fact of the possible long preservation of the tubercle bacilli in river-water. So long as they remain living, external conditions can restore to them the virulence which they have lost.

lin Cochez* (1883) states that the number of tubercle bacilli preserved on thre en and handkerchiefs appears to increase in the sputum preserved for enla e weeks, as shown microscopically; the dimensions of the bacilli are that ged, especially in the sputum kept in the incubator. He states also partic Tappeiner produced tuberculosis in dogs by causing them to inhale dried

Corn es of sputum.

tubercle et† (1907) summarized his conclusions upon the biology of the may be c bacillus by stating that we are dealing with a microörganism which fluences se alled a strict parasite. Its resistance to external injurious in- as a hard en ems to depend upon the wax-like substance which surrounds it non-spore-be velop. This gives it a middle place between the spore- and the 80° C., is not ring organisms. It is destroyed in a few minutes at 70° and sunlight—being susceptible to cold, even when frozen; is readily injured by killed in a few minutes to a few hours; diffused light requires

* Cochez, A.: "De la recherche du bacille de la tuberculose dans les crachets," Compt. rend. soc. biol., Paris, 7 s., vol. v, 1883, p. 365.

† Cornet, G.: "Die Tuberkulose," 2 vols., Wien, 1907.

several days for this action. When dried in not too thin layers, it lives for several months to a half a year. On account of its slow growth upon artificial culture-media it cannot withstand the active influence of the bacteria of decomposition, which overgrow it and finally destroy it. A great number of chemical substances prevent its development and influence its virulence. Against external influences it lives a comparatively short time; even under favorable conditions, upon nutrient media, at a favorable temperature, it dies in a short time—upon serum after half a year, in glycerin-agar in four to six weeks.

The death of cultures seems to be quicker the more luxuriant the growth. The vitality of the tubercle bacillus in human and animal organisms seems to be relatively a limited one. The majority of the tubercle bacilli in phthisical sputum and in cavities are unable to develop; also, many of the bacilli found in the tissues are probably dead. This view is confirmed by the difficulty of obtaining cultures from particles of old tissue containing innumerable bacilli.

De Souza* (1889) did some work upon the effects of inhalation of powdered tuberculous material. The following are the results of a series of experiments made by Souza with the assistance of M. Gallois:

The walls of cavities were dried in the incubator, reduced to fine powder, and then insufflated into guinea-pigs by way of irritating the respiratory tracts of the animals. Twelve of the fourteen animals so treated became tuberculous.

While these inhalations were not prolonged, they penetrated into the bronchi, because one of the nares of the animal was closed, and through the other the bacterial powder was directly insufflated with a rubber bag with the aid of the inspirations of the animal. Each guinea-pig had no more than a few inhalations, yet twelve out of fourteen died with tuberculosis. The lungs and tracheobronchial glands were invariably affected.

De Souza states that these experiments confirm those of Villemin, Sc[illegible] and Fischer, and demonstrate the danger of inhalation of tuberculous [illegible]ER-ducts when dried.

De Thoma† (1886) found tuberculous sputum virulent at the end [illegible] months' desiccation. According to him, the virulence disappeared [illegible] result of putrefaction at the end of ten or eleven days.

Di Donna‡ used agar cultures about one month old. The cul[illegible] virulent for guinea-pigs, causing their death after hypodermic [illegible] about two months.

The cultures were exposed on a large balcony in the upp[illegible]

KILLED [illegible]VING—	
[illegible]ds Ab-[illegible]ess [illegible]ocal.	Other Diseases.
..	..
..	..
..	.. es
1	..

* De Souza, A.: "Sur la propagation de la tuberculose," Cong. [illegible] tuberculose, 1st sess., 1888, 1889, p. 325.

† De Thoma (as quoted by Straus): Ann. univ. di. med., July, [illegible]

‡ Di Donna, A.: "Untersuchungen über die Immunisierung mi[illegible] abgetöteten oder abgeschwächten Milzbrand- und Tuberkelbacille[illegible]ion and their [illegible]irty-1 Abt., vol. xlii, 1907, pp. 642–646.

[illegible]v, 1898, p. 13[illegible].

Hygienic Institute of the Royal University at Naples. Experiments were conducted in the summer-time, when the temperature in the sun reached 42° C. The cultures were thus exposed every day from 9 o'clock in the morning until sundown. After an exposure of direct sunlight for eight days, cultures of tubercle bacilli were sterile. After six days of such exposure some of the injected guinea-pigs became infected. Cultures exposed for six days in another season of the year, viz., toward the end of autumn or in the winter, remained infectious for guinea-pigs.

The tubercle bacillus becomes decidedly attenuated, however, so that the process in inoculated animals lasts longer.

Dixon* (1908) raises the question whether the tubercle bacillus may not be found in sewage, and, if so, to what extent. Several methods were employed to demonstrate the presence of the tubercle bacillus in sewage. A bacillus, morphologically resembling the tubercle bacillus by tinctorial methods, was found.

The first recorded experiments upon the effect of sunlight upon the tubercle bacillus are those of Feltz.† He made a mixture of soil and tuberculous sputum, rich in tubercle bacilli. This was exposed to the direct rays of the sun, commencing on September 13, 1887. After one hundred and thirty-seven days' exposure this material caused tuberculosis when introduced into guinea-pigs, but beyond this time it lost its virulence. The same author makes the extraordinary statement that a portion of the same mixture, when exposed to changing climatic and atmospheric conditions as they occur naturally, retained its virulence for but a little over two months. The mixture was subjected to the inclemencies of the weather by exposure in a box, the lid of which was pierced with numerous holes.

Galtier‡ (1888) caused the disease by subcutaneous, intraperitoneal, and ha[illegible]venous inoculations of tuberculous matter dried at 30° C., or by in[illegible]tion of tuberculous lesions into the respiratory passages, dried for tul[illegible], thirty, and thirty-eight days; well-marked tuberculosis has been [illegible]d by the author by inoculations of dried matter, exposed to the temtub[illegible] of the laboratory, to the air and light, after twenty, twenty-five, [illegible]y days. At the expiration of this period he has always found it days[illegible]ective. The sojourn in running water or in stagnant water Ehrl[illegible] tuberculous virulence intact for a long time. In the previous

S
days
T
in one
Fo
in two

amuel G.: "May Not Drinking-water Polluted with Sewage be One [illegible]semination of the Tubercle Bacillus?" Jour. Am. Med. Assoc., vol. li, [illegible]p. 380.

[illegible]imental et clinique sur le rôle des pousieres Bacillares dans la contagion [illegible]et sur la durée de la virulence de ces pousieres, Nancy, 1890.

"Dangers des matières tuberculeuses qui ont subi la dessiccation, le [illegible]l'eau, la congélation, les alternatives d'elevation, et d'abaissement de [illegible]putrefaction cadavérique dans la terre," Cong. pour l'étude de la [illegible]C[illegible]888, p. 305.

* Ca
Cong. pc

year the author stated that he had transmitted the disease to a number of rabbits by their inoculation with tuberculous spleen, preserved in small fragments for eight, ten, fifteen, and seventeen days in water varying from 3° to 8° C., in a state of more or less putrefaction. He obtained the same results with tuberculous matter of pigs and cows which had preserved its virulence in running and stagnant water at a temperature of +17°, +13°, and 0° C.; after fourteen days' immersion, the virulence has remained intact in these lesions; those immersed in stagnant water, and those submitted to advanced putrefaction, have produced tuberculosis very slowly in rabbits; finally, a latent tuberculosis was obtained in the guinea-pig by inoculation of tuberculous matter of a cow kept two months in running water, the temperature of which varied between +4° and +10° C., but the four last days the water was frozen to —3° C. It is not doubtful that the tuberculous virus, fresh or dried, can be preserved in fountains, troughs, pools, etc., and thus return to some organism to perpetuate the disease.

Gardiner* (1898) records experiments made at Colorado Springs, Col., upon the effect of sunlight and drying on the infectiousness of tuberculous sputum. The tuberculous sputum made use of by him was found to be infectious by inoculation into rabbits, producing general tuberculosis within twenty or thirty days. This sputum was exposed to the direct rays of the sun for varying periods and at different situations, with a background of sand, stone, or wood. After exposure to the sun the sputum was rubbed up with sterilized water and inoculated into the thigh of a guinea-pig. The animal was killed in thirty to forty days after inoculation. Some 13 guinea-pigs were inoculated with 0.3 c.c. of sputum and water each. The sputum was exposed to the direct sunlight for one and three-quarter to twelve hours (twenty-four hours in the table).

EXPERIMENTS TO DETERMINE THE EFFECT OF SUNLIGHT UPON TUBERCULOUS SPUTUM. ANIMALS USED, GUINEA-PIGS. SEAT OF INOCULATION, LEFT THIGH.

Number of Animals Inoculated with Exposed Sputum.	Length of Exposure.	Number Inoculated with Non-Exposed Sputum.	Of which Died within Twenty Days with—		Of which Died or were Killed after Twenty Days, Having—			
			Local Tuberculosis.	Other Diseases.	General Tuberculosis.	Glands Generally and Spleen Affected.	Glands or Abscess Local.	Other Diseases.
1	1¾ hours	..	..	..	1	..	..	..
4	2 hours 5 minutes	..	2	1	..	1	..	..
2	24 hours	..	2	..	..	..	..	..
..	..	6	1	3	1	..	1	..

* Gardiner, Charles Fox: "The Dangers of Tubercular Infection and their Arrest by Climatic Influences" Am. Jour. Med. Sci., Phila., vol. cxv, 1898, p. 137.

Graziana* experimented with the tubercle bacilli upon the hands of persons affected with pulmonary tuberculosis and having the bacilli in their sputa.

Out of 8 tuberculous patients examined, 4 had the bacilli on their hands. Three hours after washing their hands with soap and water, 3 of the 4 still had the bacilli on their hands. Out of 6 non-tuberculous patients, he found the bacilli on the hands of 4. After shaking hands with 6 tuberculous patients at different times, he found tubercle bacilli on his hands twice.

Hance† (1898), in a brief note, states that sputum obtained from a pronounced case of tuberculosis, with which he inoculated 6 guinea-pigs, in eight weeks produced generalized tuberculosis in all of them. The remainder of the sputum was well corked in large-mouthed bottles, half full, and kept in a dark closet for seventeen months. It was still fluid; it was thoroughly mixed and inoculated intraperitoneally and subcutaneously into two guinea-pigs; the first died in forty-eight hours of sepsis; the second was killed at the end of thirty days. Autopsy showed no tubercular lesions.

The sputum was then mixed with water and centrifugalized and examined microscopically, with the result that the bacilli were found in a fragmentary state, although the fragmented mass was acid-resistant; this centrifugalized sputum was also inoculated subcutaneously into two guinea-pigs with negative results.

He concludes that the tubercle bacilli were no longer viable, and the question is raised, Does sputum kept in a liquid state for so long a time develop toxin which is inimical to the life of the bacilli?

Hill‡ (1903) used tuberculous sputum containing great numbers of tubercle bacilli. Glass rods were inoculated in sets, one rod in each set from each culture and each culture coming from a different source. Several sets of rods were exposed in a drying box, arranged to admit diffused daylight and to permit slow diffusion of air. The box stood in the laboratory, subject to ordinary room fluctuations of temperature and humidity.

The survival of the bacilli was tested at the end of various periods by inoculation into guinea-pigs. The shortest period tested was sixteen days, giving a negative result. Most of the tests were from twenty-seven days upward; all were negative.

Jousset§ (1900) states that, apropos of a recent communication from the prefecture of police defending spitting on the street, the study of the action of light upon the tubercle bacilli was undertaken.

* Graziani, A., 1905: "Sulla possibilita e frequenza d'infezionemer mezzo delle mani dei tuberculosi," Ann. d'Ig. sperim., vol. xv, No. 4, 709–723.

† Hance: "A Single Test of the Virulence of Sputum Kept Many Months," Med. ws, N. Y., vol. lxxiii, 1898, p. 787.

‡ Hill, Hibbert Winslow: "The Distribution of B. diphtheriæ and B. tuberculosis in t ooms Occupied by Patients Suffering from these Diseases," Proc. 30th Ann. Meet- Am. Pub. Health Assoc., N. Orl., December 9–12, 1902.

§ Jousset, P.: "Action de la lumière solaire et de la lumière diffuse sur le bacille h contenu dans les crachats tuberculeux," Compt. rend. Soc. de biol., Paris, Cong. po 32), 1900, pp. 884–885.

Series A.—Five guinea-pigs inoculated subcutaneously with tuberculous sputum. The control died on the twenty-eighth day. It lost 160 grams. The spleen is small; numerous tubercle bacilli are present in the inoculation abscess. Pyrexia ranged between 40° and 40.5° C.

Guinea-pig 1: Injection of sputum exposed one hour to sunlight and incompletely dried; killed on the sixtieth day. Increase of weight, 55 grams. Persistence of inoculation ulcer in which tubercle bacilli were found.

Guinea-pig 2: Inoculation of sputum exposed to sunlight for five hours and completely dried; killed on sixty-third day. The animal had increased in weight 160 grams, and the tubercle bacillus was not found.

Guinea-pig 3: Inoculation with sputum exposed to diffuse light for seven hours. Death after twenty-four days; increase of weight, 100 grams. No tubercle bacilli.

Guinea-pig 4: Inoculation with sputum exposed for four hours and completely dried in diffuse light. Death by traumatism on thirtieth day; increase of weight, 60 grams. Tubercle bacilli absent.

In this first series the sputum was always sterile when it had been exposed for at least four hours to direct or diffuse sunlight. If animal No. 1 showed tubercle bacilli in the inoculation ulcer, it was because the sputum had been exposed but one hour to sunlight.

Series B.—Inoculation of five guinea-pigs. The control died on the nineteenth day. Numerous tubercle bacilli were found in the inoculation wound and in the spleen.

Guinea-pig 1: Inoculation with sputum exposed four hours to diffuse light and completely dried; killed on the seventy-seventh day; increase of weight, 70 grams. Tubercle bacilli found in the inoculation wound.

Guinea-pig 2: Inoculation with sputum exposed for seven hours to diffuse light; killed on the seventy-seventh day. Increase of weight, 60 grams. A few tubercle bacilli were found in the inoculation wound.

Guinea-pig 3: Inoculation with sputum exposed to sunlight for one and a half hours; killed on sixty-third day. Increase of weight, 65 grams. Tubercle bacilli were found in inoculation wound. Small non-tubercular abscesses on spleen.

Guinea-pig 4: Inoculation with sputum exposed to sunlight for one hour; killed on fifty-sixth day. Tubercle bacilli absent.

In this series, with the exception of animal No. 4, all presented the tubercle bacillus at the site of inoculation, although the sputum had been exposed to diffuse light for from four to seven hours. The animals not only fattened, but they had no rise of temperature and presented all appearances of health.

Series C.—Three guinea-pigs inoculated. The control died on the thirty-second day. It had had fever and showed a number of tubercle bacilli.

Guinea-pigs 1 and 2 inoculated with sputum for one and a half hours to sunlight and completely dried. No. 1 lost 40 grams of weight and showed a number of tubercle bacilli. No. 2 lost 65 grams of weight, but showed no tubercle bacilli at the site of the inoculation.

Conclusions.—In a certain number of cases tuberculous sputum is completely sterilized by the action of light; it is always attenuated, since health is apparently preserved, and weight increased habitually, and since the tubercle bacillus is not found except at the site of inoculation. The time of exposure to light appears to have a great influence upon the bactericidal action of this agent.

Kirstein* says that it is possible for tuberculous sputum, in the form of dust, to cause infection, as indicated by a number of pupils of Flügge and Cornet. He undertook a number of investigations to determine the viability of the tubercle bacillus in dust from various sources. He first collected dust from the papers in the city clerk's office. This was passed through a sieve into two aspirator flasks, which were connected with a bell-jar, on the floor of which were placed twelve to fourteen ordinary plates; the bell-jar had an opening, through which a spray was passed charged with culture of tubercle or with an emulsion of tuberculous sputum. The fineness of the spray was extreme, and the operation was conducted in such a manner that upon the control plates only one tubercle bacillus in twenty or thirty fields of the microscope was found.

Examination was then made to determine if the bacilli thus deposited were living, either at once, or after they have swept the surface of the plates, impregnated with droplets of spray by the introduction of a current of air. After two, three, five, or eight days the bell-jar that had been exposed to the light was removed, and some of the plates of bouillon were used to inoculate guinea-pigs intraperitoneally, in doses of 5 c.c.

The second procedure consisted in collecting in the first flask the dust that had been infected and passing it, by means of a current of air, into the liquids which were inoculated into guinea-pigs.

Kirstein summarizes his results in the following table:

DURATION OF THE LIFE OF THE TUBERCLE BACILLUS IN DUST CAPABLE OF FLYING ABOUT.

Kind of Dust.	Time of Death of the Tubercle Bacillus Clinging to Dust.†
Dust from paper and books infected with fine spray containing tubercle bacilli	Between 8 and 14 days
Sputum-dust containing tubercle bacilli	" 4 " 7 "
Cloth fibers containing tubercle bacilli	" 5 " 10 "
Street-dust containing tubercle bacilli	" 3 " 8 "

* Kirstein, Fritz: "Ueber die Dauer der Lebensfähigkeit von Tuberkelbacillen an flugfähigen Stäubschen," Zeit. f. Hyg., vol. 1, 1905, p. 186.

† The figures to the left indicate positive results, those to the right negative results, according to animal experiments.

The author concludes in part that he obtained unexpected results in that the life-history of the tubercle bacillus in dust is very limited.

Koch* (1890) says that: "The influence of light is especially important. For years we have known that direct sunbeams would kill germs quickly, and I have found that tubercle bacilli live but a few minutes or few hours in sunlight, according to the thickness of the exposed layer, but even dispersed daylight has the same influence, though it is slower, for cultures placed near a window die in five to seven days."

Koch† (1892) found that, by drying, the virulence of infectious sputa is not lost. He inoculated 4 guinea-pigs with two-weeks-old dried sputum; later, 4 other guinea-pigs with dried sputum preserved for four weeks, and later, 4 other guinea-pigs, with sputum dried for eight weeks, with the result that tuberculosis developed the same as when the inoculations were made with fresh material.

The author concludes that in the soil, clothing, etc., dried tuberculous sputum retains its virulence for a long time, and, when taken in the lungs in the form of dust, it can produce tuberculosis.

Lösener‡ (1896) conducted a number of experiments in order to determine the viability of the tubercle bacillus when buried in the ground, and came to the conclusion that in cadavers it remains virulent only up to three months. This longevity appears to be independent of whether the cadaver is in contact or not with the ground-water. After four months virulent tubercle bacilli were not found in cadavers buried in the sand, loam, gravel, and swamp, and also independently of whether the ground-water is present for a longer or a shorter period. In these experiments the tuberculous organs were placed in the cadavers of hogs dead of hog-cholera, which were then buried under various conditions. Portions of the buried organs were later examined microscopically for the tubercle bacillus. Portions of the earth surrounding the cadavers, the organs, the ground-water, the cloth wrapped around the bodies, and splinters of wood, were then inoculated into animals, and the results recorded. Some of the animals remained well and others died of septicemia or malignant edema.

Maffucci§ (1891) sterilized silk threads, saturated them in bouillon culture of chicken tuberculosis, and placed them under a bell-jar to dry. Calcium oxid was placed under the bell-jar to facilitate drying.

* Koch, R.: "Ueber bakteriologische Forschung," Verhandl. d. internatl. med. Congresses, 10 sess., vol. i, 1890, p. 35.

† Koch, Robert: "Die Aetiologie der Tuberculose," Berl. klin. Wchnschr., vol. xix, 1892, p. 229.

‡ Lösener, W.: "Ueber das Verhalten von pathogenen Bakterien in beerdigten Kadavern und über die dem Erdreich und Grundwasser von solchen Gräbern angeblich drohenden Gefahren," Arb. a. d. k. Gesundheitsamt, vol. xii, 1896, p. 448.

§ Maffucci, Angelo: "Die Hühnertuberculose," Experimentelle Untersuchungen, 10. "Einfluss der trockenen Luft auf die Culturen," Ztschr. f. Hyg., Leipzig, vol. xi, 1891, p. 461.

(1) Some of these threads were at once inoculated intraperitoneally in chickens, which died after five months with general tuberculosis.

(2) After fourteen days of drying, the threads were inoculated intraperitoneally in chickens, which died of general tuberculosis after seven months.

(3) After one month of drying, chickens inoculated the same way died of general tuberculosis after ten months.

(4) After two months of drying, chickens inoculated in the same way were killed after ten months. Autopsy showed no lesions in the liver or peritoneum; only a small external nodule was found in lung, which contained tubercle bacilli.

Malassez and Vignal* (1883) endeavored to place tubercular sputum under natural conditions. Vignal dried a certain quantity of the sputum, in which he had first demonstrated the presence of tubercle bacilli, in a flat vessel. After being desiccated, the sputum was pulverized, moistened, then desiccated again, and the process repeated. After twelve days and eight successive moistenings and desiccations Vignal again found the tubercle bacilli, and they seemed to be in as great a quantity as in the fresh sputum. In order to determine whether they preserved their pathogenic activity Vignal inoculated guinea-pigs and reserved the report of the results for a later communication.†

The inoculations of the guinea-pigs were made subcutaneously on the abdomen of two animals. One of the animals died in seven days without evidence of tuberculosis; the other gained weight, but finally died. At the autopsies the spleen, liver, lungs, mesentery, and glands were infiltrated with tuberculous nodules. From the experiments the authors conclude that tubercular sputum falling upon the ground, even after being dried and moistened several times, may still be a source of very great danger for persons not infected with tuberculosis.

McClintic‡ (1906) found that formaldehyd usually destroyed the infectiousness of tuberculous sputum exposed on threads and on pieces of carpet. A drop or two of sputum containing many bacilli were placed on the pieces of carpet or thread. These were dried in the incubator for one hour, and then taken to the railroad station and exposed in various parts of sleeping-cars that were used for the purpose of these experiments. If the guinea-pigs developed lesions, the results were considered positive. No secondary inoculations were undertaken.

* Malassez, L., and Vignal, W.: "Sur la persistance des bacilles dans les crachats des phthisiques," Compt. rend. soc. de biol., Paris, 7 s., vol. v, 1883, p. 367.

† Malassez, L., and Vignal, W.: "Persistance de la puissance pathogénique des bacilles dans les crachats desséches des pathitiques," Compt. rend. soc. de biol., Paris, 7 s., vol. v, 1883, p. 650.

‡ McClintic, Thomas B.: "The Limitations of Formaldehyde Gas as a Disinfectant, with Special Reference to Car Sanitation," Hyg. Lab. Bull. No. 27, U. S. Pub. Health and Mar. Hosp. Serv., Washington, 1906.

Migneco* adopted the method of spreading sputum, rich in tubercle bacilli, on linen and woolen cloths, stretching them on a frame, and exposing them to the direct rays of the sun. The experiments were commenced on July 31, 1894, and ended September 22, 1894. After different lengths of exposure, either small bits of cloth were cut from the frames, moistened, and then inoculated subcutaneously into guinea-pigs and rabbits, or the cloth was soaked in sterile water and squeezed out as thoroughly as possible, and this liquid injected into the animal. Migneco's conclusions were as follows:

(*a*) Sunlight exercised a deleterious effect on the tubercle bacillus, just as it does on other bacteria.

(*b*) Tubercle bacilli, as found in tuberculous sputum, and spread on linen or woolen cloths, are not able to withstand the influence of direct sunlight for more than twenty-four hours to thirty hours, provided the sputum is not spread in too thick a layer.

(*c*) The virulence of the tubercle bacillus diminishes gradually after ten to fifteen hours. However, it is still able to produce localized tuberculosis. After twenty-four to thirty hours it entirely loses its virulence.

Mitchell and Crouch† (1900) began some experiments in the latter part of September, 1897. The plan was to deposit on a sandy soil as much tuberculous sputum as a patient in the second or third stage of phthisis usually expectorates when walking about. This was then exposed to the direct rays of the sun for varying lengths of time, and its virulence tested by the inoculation of guinea-pigs.

The authors were fortunate in securing for their experimental work a sputum that was remarkably free from all bacteria except tubercle, and was expectorated in large quantities. The technic was as follows: The morning sputum was allowed to remain for two hours in a sterilized filter-paper and funnel, to drain off as much saliva as possible. The soil was placed in the lower half of a Petri dish and sterilized. Four grams of sputum were then weighed, placed on the soil, and exposed to the sun's rays. When the allotted hours of exposure had terminated, the sputum, which after the first several hours of exposure had formed a firm crust and could be easily lifted en masse, was taken from the soil with a sterile spatula and dissolved in 6.5 c.c. of sterilized distilled water: 1 c.c. of this mixture was injected intraperitoneally.

In order to test the virulence of the sputum 2 guinea-pigs were inoculated

* Migneco, Franz: "Wirkung des Sonnelichtes auf die Virulenz der Tuberkelbacillen," Arch. f. Hyg., vol. xxv, 1895, p. 361.

† Mitchell, William C., and Crouch, H. C.: "The Influence of Sunlight on Tuberculous Sputum in Denver: a Study as to the Cause of the Great Degree of Immunity Against Tuberculosis Enjoyed by those Living in High Altitudes," Journ. Path. and Bact., vol. vi, 1900, p. 14.

as controls. One died after twenty days and the other after six weeks, both presenting the typical lesions found in tuberculous guinea-pigs. With the sputum, which was exposed to the different insolations, two pigs each were inoculated. The hours of exposure were as follows: one, two, four, seven, ten, fifteen, twenty, twenty-five, thirty, thirty-five, forty-five, fifty-five hours. At the autopsies, sections were made of one or more of the organs and examined for tubercle bacilli, and provided this test failed, sections were stained and studied histologically.

The autopsies revealed that sputum which had been exposed up to thirty-five hours was still virulent. However, in only one of the two animals injected with the sputum, insolated for thirty-five hours, was tuberculosis produced. The other animal was tuberculous, it is true, but from what follows it will be seen that this animal suffered from inhalation tuberculosis.

An abstract from the autopsy of the first pig inoculated with the thirty-five-hours material shows the following: Spleen and liver contain few tubercles: tubercle bacilli demonstrated in sections of the spleen; histologically, typical tubercles were present, with the exception that there were no giant-cells. This guinea-pig, on December 9th, gave birth to two young about seven weeks after she was inoculated, and at the time she was killed she was fairly well nourished and suckled her young with apparent comfort. The tuberculous virus after this long exposure, although it could still produce tuberculosis, had greatly lost its virulence. The two pigs born were killed about a month later, and were found to be healthy and fairly well nourished.

An abstract from the autopsy of the second animal, inoculated with the material that had been exposed for thirty-five hours, shows the following: Peritoneum clear; liver and spleen normal; lungs contain a few tubercles; bronchial glands enormously enlarged. Sections of spleen show no tubercles; histologically, normal tissue found. Sections of bronchial glands show tubercle. Diagnosis, inhalation tuberculosis.

The animals which were inoculated with the sputum exposed from one to twenty-five hours were all tuberculous, with the exception of one animal, injected with the seven-hour sputum, which died on the ninth day of an acute sepsis.

In the sections of the organs taken from the animals which were inoculated with sputum exposed from one to seven hours tubercle bacilli were present in such great numbers that it seemed almost incredible that animals which are so susceptible as guinea-pigs were able to live as long as they did. From the ten-hour up to the thirty-five hour exposure tubercle bacilli could be demonstrated only after considerable search, and in some cases, where characteristic lesions were present, histologically, no tubercle bacilli could be found.

The sputum exposed above thirty-five hours, *i. e.*, forty-five and fifty-five hours, failed to cause tuberculosis. In one of the forty-five-hour pigs all organs were free from tubercular disease, except the lungs, which contained a few tubercles, and the bronchial glands were enormously enlarged and tuberculous. According to Koch, this must be classified as inhalation tuberculosis.

One or two of the animals of the earlier injections, which were very feeble and emaciated, and would unquestionably have died in a short time, were killed to obtain a pure culture of tubercle bacilli. Out of forty tubes inoculated with dissected-out tubercles, the authors succeeded in starting but one pure culture.

A summary of these results show:

1. That the tubercle bacillus, as it is expectorated on a sandy soil, is still virulent after thirty-five hours' exposure to the sun's direct rays in the altitude of Denver, Colo.

2. That such sputum has suffered but little diminution in virulence after twenty hours' exposure.

3. That after from twenty to thirty-five hours' exposure, the virulence is gradually diminished, and finally lost if the exposure extends beyond the last-mentioned time.

Mohler and Washburn* found that, as a result of their investigations, in certain instances tubercle bacilli may be transformed not alone in form, but in pathogenicity and cultural characteristics as well. Many virulent cultures may be attenuated by continued artificial cultivation. The opposite change, increasing the virulence, may be obtained for some cultures with a low order of original virulence.

Muschold's† investigations were based upon the fact that the tubercle bacillus is resistant on account of the fatty acid and waxy substances which form a hard shell, protecting it against dryness. He considers, further, that tuberculous sputum is the principal carrier of infection. He determined the length of time it remains virulent in natural river-water, in sewage water, and in arable soil. For this purpose he used water of the Spree at Berlin, dirty surface water, sewage from the Berlin sewers, canal sewage, etc. The media under observation were kept partly in the dark and partly in diffused daylight, and partly also in midday sunlight. It was further exposed to various influences of the weather, including frost, snow, rain, and heat. Guinea-pigs were used, and the experiments controlled.

* Mohler, John R., and Washburn, Henry J.: "The Susceptibility of Tubercle Bacilli to Modification," Bureau Animal Industry: Twenty-third Ann. Rep., 1906, pp. 113–163.

† Muschold, P.: "Ueber die Widerstandsfähigkeit der mit dem Lungenauswurf herausbefördeten Tuberkelbacillen in Abwässern, im Flusswasser, und im kultivierten Boden," Arb. a. d. kais. Gesundheitsamt, vol. xvii., 1900, Heft. 1.

As a result of his observations Muschold comes to the conclusion that the vitality of the tubercle bacillus in sputum lasts for a number of months, and is the same whether the sputum is dried or whether it is in various media, such as sewage waters, soil, etc. He obtained similar results irrespective of the presence of other harmful conditions, such as frost, snow, rain, sunshine, fermentation, etc. He believes that the tubercle bacillus in sewage-polluted river-water may remain infectious half a year. He considers, in conclusion, that sputum should always be disinfected before allowing it to run into sewers or to pollute surface waters, and that this disinfection is best done at the boiling temperature.

Nuttall is quoted by Annett* as follows: "Experiments by Nuttall seem to indicate that, under favorable temperature circumstances, tubercle bacilli may even multiply in tubercular sputum outside the body."

Park and Williams† (1905) state that, according to experimental investigations, the virulence of dried tuberculous sputum is not suddenly, but gradually, lost, a certain proportion of it retaining its specific infective power under ordinary conditions, as in a dwelling-room, for at least two or three months, and occasionally for a year or more.

Petri‡ (1890) states that "we have exhumed tubercle bacilli capable of producing infection after three months." The work was done upon human cadavers, which Petri thinks may account for the difference in his results and those of Schotellius, who worked with smaller animals.

Ransome and Delepine§ (1894) record some interesting work. The following table is reproduced in full from the original:

TABLE 1.

Experiment No.		
3.	1.	Rabbit inoculated in peritoneum with fresh sputum. Killed fifty-five days after. Showed well-marked tuberculosis.
7.	2.	Rabbit. Sputum exposed to light and air forty-five days in June and July. Showed no tuberculosis after eighty-six days.
8.	3.	Rabbit. Sputum exposed in air-shaft in dusk at the same time. Showed slight tuberculosis after eighty-six days.
11.	4.	Guinea-pig. The same sputum exposed at the same time, in air and light, inoculated under the skin. Showed no distinct tubercle in eighty days.
12.	5.	Guinea-pig. Same method, only in dusk. Showed advanced tuberculosis in eighty days.
58.	6.	Guinea-pig. Another sputum exposed in April for sixteen days to little or no air in darkness. Gave well-marked tubercle after forty-two days.

* Annett, H. E.: "Tubercular Expectoration in Public Thoroughfares," Jour. State Med., vol. xi, 1903, p. 462.

† Park, William H., and Williams, Anna W.: "Bacteria Pathogenic to Man Individually Considered; The Bacillus of Tuberculosis; Viability," 1905.

‡ Petri: Verhandl. d. internatl. Med. Cong., vol. v, 1890, p. 126.

§ Ransome and Delepine,: "On the Influence of Certain Natural Agents on the Tubercle Bacillus," Proc. Roy. Soc., London, vol. lvi, 1894, p. 51.

The authors made further series of experiments to determine how short a period of exposure to air and light would destroy the pathogenic action of the bacillus. Guinea-pigs were employed as test-animals.

In the first instance pure cultures were prepared and found to be active by frequent inoculations. The cultures were spread in thin layers on sterilized paper. They were exposed in a glass room with free access to air and light for diminishing periods of fourteen, ten, six, four, and two days, respectively. The authors note that only one of these experiments can be relied upon, and that in this case, after four days' exposure to air and twelve and a quarter hours of sunshine, there was no result from the inoculation.

These observations, though not in any way conclusive, are in accord with those of Koch,* and they encourage the belief that even short exposures of the tubercle bacillus, even in sputum, to air and light, might render it innocuous.

In the next series it was determined to allow tuberculous sputum to dry—(*a*) in air and light; (*b*) in air and darkness; (*c*) in a close cupboard.

Fresh sputum, rich in bacilli, was obtained and exposed in watch-glasses. Specimen *a* was dry in four days; (*b*) in eight days; and (*c*) in nineteen days.

Specimens (*a*) and (*b*) were closed up as soon as they were dry, and kept until (*c*) was ready; then portions of the sputum was scraped off and inoculated into guinea-pigs. Table 3 gives the results:

TABLE 3.

No.		
117.	1.	Sputum (*a*) inoculated subcutaneously into two guinea-
118.	2.	pigs, killed sixty-four days afterward, gave well-marked tuberculosis.
119.	3.	Sputum (*b*), similarly inoculated, showed no results fifty-
120.	4.	three days after.
126.	5.	Sputum (*c*) gave well-marked tuberculosis fifty days afterward.

No decided conclusion can be drawn from this series of experiments, for while the thickness of the layer of sputum might account for the continued virulence of 1 and 2, the non-virulence of 3 and 4 is not likely due to the eight days' exposure to air and darkness.

Conclusions.—If the results obtained by the authors are confirmed by others, they may show: (1) That finely divided tuberculous matter, such as pure cultures of the bacillus or "tuberculous dust," in daylight and in free currents of air, is rapidly deprived of virulence; (2) that even in the dark, although the action is retarded, fresh air has still some disinfecting influence, and (3) that in the absence of air, or in confined air, the bacillus retains its virulence for longer periods of time.

* Verhandl. d. internat. med. Cong., Berlin, 1890, vol. i, p 35.

Schill and Fischer* (1884) were among the first to conduct a large series of experiments upon the viability of the tubercle bacillus. Their work is often quoted as proof of the unusual vitality of the tubercle bacillus. These investigators considered, with Koch, at that time, that the tubercle bacillus had a spore which corresponded in its resistance to the anthrax spore. They used sputum which, under the microscope, was rich in tubercle bacillus "spores." This was dried at room temperatures upon glass plates. The dried mass was scraped off with a knife into cork-stoppered bottles. They found that such dried sputum invariably produced positive results in guinea-pigs of after ninety-five, as well as one hundred and twenty-six, days.

They found some difficulty in finding sputum for their experimental purposes with and without the tubercle "spores." However, further experiments showed that the dried sputum finally lost its infective power after one hundred and seventy-nine days.

In two guinea-pigs the tuberculous sputum was infective after ninety-five days' drying; of three guinea-pigs inoculated with tuberculous sputum dried for one hundred and forty-three days, only two became tuberculous; while of three guinea-pigs inoculated with tuberculous sputum dried for one hundred and eighty-six days, only one became tuberculous. Four guinea-pigs inoculated with tuberculous sputum dried for two hundred and twenty-six days remained well. They conclude, therefore, that the death of the tubercle bacillus in these sputa is not synchronous. They do not state the lesions or other details in the guinea-pigs said to be positive.

They then tried a number of experiments to determine the thermal death-point of the tubercle bacillus, and found that 100° C. of dry temperature did not surely destroy the virulence of tuberculous sputum, whether dry or moist; also the effect of various chemical substances. They came to the conclusion that sublimate solutions are not to be depended upon for this purpose, whereas carbolic acid is a good disinfectant for tuberculous sputum. They recommended 5 per cent. solution, using equal quantities of the solution and the sputum, and allowing twenty-four hours' contact.

Rickards, Slack and Arms have reported† a series of experiments to ascertain the longevity of B. tuberculosis in sputum under varying conditions of light and moisture.

At first the experiments were conducted in tenement-house rooms selected to represent the varying conditions: (*a*) sunny and dry; (*b*) diffuse light and dry; (*c*) dark and dry; (*d*) dark and damp (basement), the sputum used being a mixed sample from an institution. The inconsistent results ob-

* Schill, E., and Fischer, Bernard: "Ueber die Desinfection des Auswurfs der Phthisiker," Mitth. a. d. kais. Gesundheisamt, vol. ii, 1884, pp. 131–146.

† "Longevity of Bacillus Tuberculosis in Sputum," read before the American Public Health Association at Winnipeg, September, 1908.

tained in these first experiments led to a repetition, under new conditions, sputum from a single individual which had previously been tested as to virulence being used, and all the tests carried on in the laboratory approximating the above conditions as closely as possible.

In (*b*) living and virulent tubercle bacilli were found up to one month's exposure.

In (*c*) they persisted as far as material had been prepared, so no end point was reached, although experiments were carried on up to eighty-five days' exposure. (Experiments are being repeated.)

In (*a*) and (*d*) experiments are under way.

All this work has been done by animal inoculation. Results have been obtained from 380 inoculated animals; 110 are under observation from (*a*). Material for (*c*) and (*d*) is exposed and inoculations will be made at the proper time.

The results of the experiments so far concluded indicate that tubercle bacilli retain life and virulence in sputum much longer than is generally believed possible, and that the sputum of tubercular patients cannot be too carefully cared for.

Sawizky* (1891), in consequence of the well-known important rôle played by tuberculous sputum in the etiology of tuberculosis, has contributed, through his specific investigations, to the knowledge concerning the duration of virulence in such sputa.

The sputum was dried and preserved under the conditions usually prevailing in dwellings. Guinea-pigs and rabbits served as test-animals.

The author divided his investigations into two groups. In the first group were included the experiments with sputa dried and preserved in the dark; in the second, those with sputa which, throughout the entire time, were exposed to the influence of sunlight. As a control, two guinea-pigs were infected with the fresh sputum. Upon the death of the animals the viscera were examined microscopically.

Upon the basis of his experiments the author draws the following conclusions:

(1) That sputum dried and preserved under the conditions of ordinary living-rooms retains its specific virulence for two and a half months.

(2) The virulence of such sputum is not suddenly, but gradually, lost.

(3) That under the influence of direct sunlight, tuberculous sputum loses its virulence concurrently with sputum preserved in the dark.

Schotellius† (1890) determined that tubercle bacilli in buried phthisical

* Sawizky, W.: "Zur Frage über die Dauer der infektiösen Eigenschaften des getrochneten tuberculösen Sputums," Inaug. Diss., St. Petersb. (Reviewed by Geisler), Centralbl. f. Bakteriol., etc., Jena, vol. xi, 1891, pp. 153–154.

† Schottelius, M.: "Ueber Temperatursteigerung in beerdigten Phthisikerlungen," Centralbl. f. Bakteriol., etc., Jena, vol. vii, 1890, p. 265.

lungs can retain their staining peculiarities for several years, and that such tuberculous material still preserves its virulence for the transmission of the disease to rabbits and guinea-pigs, thus raising the question whether the possible temperature gradations through putrefaction may have influence upon the buried tubercle bacilli.

The author notes some experiments made to determine the temperature gradations in buried lungs by means of a thermometer buried with the organs.

Smith and Brown* (1907) state that tubercle bacilli are usually dead after three months.

Sormani† (1886) took a certain quantity of tuberculous sputum, rich in bacilli, and agitated it for a sufficient time in a glass mortar in order to obtain a uniform distribution of the bacilli. Part was then placed under a bell-jar; part upon both sides of a piece of linen; and part placed in a glass of water, simply covered with filter-paper to permit the free exchange of atmospheric gases. These were permitted to dry, and at stated times were inoculated subcutaneously into guinea-pigs.

Sormani draws the following conclusions:

1. Tuberculous sputum dried at ordinary room temperature, in very thin layers, as it is found upon the pavements, walls, furniture, etc., maintains its virulence and vitality for more than two months; after this time the bacilli are weakened, so that at the end of four months they are lost.

2. The same sputum dried upon linen, and probably upon other goods, has not lost its virulence after six months. This is perhaps due to the fact that upon linen the sputum is spread in thicker layers.

3. The same sputum preserved in water presents much greater vitality; it is only attenuated, but not wholly destroyed, after twelve months.

Sormani‡ (1906) states that in his work three series of guinea-pigs received tubercular excretions, dried fifteen days at 35° C. in the incubator, into the respiratory tract, in the digestive tract, or beneath the skin. The infection, rapid and certain by subcutaneous inoculation, is less certain by the respiratory tract, and quite uncertain by the digestive tract.

The author concludes: (1) That the dried bacilli preserve their virulence and that there is greater danger in their introduction by the lungs than by the digestive tract. He expresses the view that the new ideas upon

* Smith, Th., and Brown, Herbert R.: "Studies in Mammalian Tubercle Bacilli. IV. Bacilli Resembling the Bovine Type from Four Cases in Man," Jour. Med. Research, vol. xvi, 1907, p. 435.

† Sormani, G.: "La vitalitá del bacillo tubercolare," Giorn. d. r. Soc. ital. d'ig., Milano, vol. viii, 1886, p. 361.

‡ Sormani, G.: "Studio sperimentale sulla virulenza degli escreati tubercolari essicati," Review by Edm. Sargent, in Bull. Past. Inst., 1908, No. 4, p. 159, Cong. de la lutte sociale contra la tuberculose, 1906

epidemiology and prophylaxis should not prompt the negligence of the old admonitions against dried sputa.

Stone* (1891) noted that tubercle bacilli, after three months in sputum, retain their power of taking stain and so are presumably alive and virulent. He also believed that he noted an increase in the number of tubercle bacilli in sputum after a period of three years. Young rabbits were inoculated with sputum-dust three years old; at the end of forty days three of the rabbits were killed, and the autopsy showed negative results. The three remaining rabbits were again inoculated, this time in the peritoneal cavity, and were killed fifty-four days later; they showed lesions which Stone interpreted as tuberculosis. He therefore concluded that, although the virulence seems to have been modified by the drying process, the bacilli were, nevertheless, alive and infective after three years. A study of the protocols of the three rabbits is not convincing that the rabbits really suffered the results of an infection with live tubercle bacilli.

Straus† (1895) states that cultures of the bacillus of human tuberculosis, aged five and six months, are only exceptionally capable of reproduction; at the end of eight or twelve months their inoculation constantly fails. If these cultures are inoculated into the cellular tissue of the guinea-pig, no lesion can be detected; the quantity of the culture inserted beneath the skin is inconsiderable; if the quantity is more abundant, an abscess at the site of inoculation is produced, without any tuberculous generalization. It will be seen, further on, that this is precisely the effect of the subcutaneous inoculation of dead tubercle bacilli.

The bacilli of avian tuberculosis preserve their vitality and pathogenic properties for a longer time in cultures upon solid or liquid media. Replanting is still effective at the end of ten months, one year, one and a half years, and, according to Maffucci, at the end of two years; but the cultures obtained in these cases are developed very slowly. Maffucci claims to have still succeeded in tuberculizing a chicken with an avian culture aged two years.

In general, the virulence of the tubercle bacillus evidently diminishes with the age of the cultures; the lesions caused by cultures aged several months are developed very slowly, and are generalized less rapidly than those resulting from the inoculation of young cultures.

Our views concerning the resistance of the bacillus of tuberculosis to a large number of agents are based upon experiments made in part with pure cultures, and in part, before the discovery of the bacillus, with natural tuberculous products.

* Stone, Arthur K.: "Why the Sputa of Tuberculous Patients Should be Destroyed; an Observation on the Viability of the Bacilli of Tuberculosis," Am. Jour. Med. Sci., vol. ci, 1891, p. 275.

† Straus, I.: "La tuberculose et son bacille," 1895, 884 pp., 4°, Paris; Biologie du bacille de la tuberculose, p. 205.

The author established that cultures of human and avian tuberculosis, developed on the surface of flasks of glycerin-bouillon, were killed, after having been exposed for two hours on a balcony to the solar rays of summer. By the side of these flasks cultures previously desiccated were exposed in thin layers on plates of glass to the solar rays; at the end of thirty minutes they had lost their vitality and virulence.

If the tubercle bacillus, under certain conditions, shows a marked resistance, to desiccation, for example, it shows great weakness under other conditions, such as heat, light, and chemical agents, such as the salts of gold. Also, in the bodies of animals and man the bacillus does not possess that vitality which is so commonly described as one of its principal attributes. It is stated, in substance, in the researches of Kitasato, that the greater part of the bacilli contained in phthisical sputum, or in the organs of cadavers, are dead bacilli. It is possible that such is the case with the bacilli contained in the covering (intimité) of the tissues, and thus is explained, in part, the difficulty that is encountered in obtaining cultures in planting tuberculous products. But if the bacillus of tuberculosis appears to be easily killed, even in the bodies of man and animals which it has invaded, the dead bacillus is far from being innocuous; the dead bacilli, as we shall come to see, persist for a long time in the organs where they have lived, and here exert an action at once inflammatory and toxic, which is one of the curious traits in the history of this microörganism.

Kitasato concluded that the greater part of the tubercle bacilli contained in sputum are dead bacilli, although there is nothing in the microscopical appearances or in the staining that prompts this conjecture. This conclusion is perhaps extreme; because bacilli planted on artificial media do not develop is not sufficient reason for concluding that they are dead. Straus has had occasion to confirm the difficulty in obtaining first cultures of tubercle bacilli; that a certain acclimatization is necessary for their regular growth on artificial media. Yet, when they had grown, inoculation in animals was constantly successful; this is positive proof that products unsuccessfully planted on artificial media do contain bacilli, both living and virulent.

It is true, Kitasato claims to have, in some cases, seen inoculation in guinea-pigs fail. But Straus has made analogous experiments with opposite results.

Straus and Dubarry* (1889) inoculated ten tubes each, containing 10 c.c. of water from the river Ourcq, and ten tubes, each containing 10 c.c. of distilled water, with small quantities of a culture of tuberculosis from glycerin-agar. The tubes were kept at temperatures of 20°, 38°, and 35° C., and at varying periods of time glycerinated bouillon was added to the tubes.

* Straus, I., and Dubarry, A.: "Recherches sur la dureé de la vie microbes pathogènes dans l'eau," Arch de méd. exper. et anat. path., vol. i, 1889, p. 5.

In two instances animals were inoculated—in one case with water of the river Ourcq after twenty-seven days' exposure; this gave a positive result in the culture; but two of the guinea-pigs showed no tuberculous lesion. In the other case the tubercle bacilli in the tube containing water from the river, kept at 38°, were positive after ninety-five days' exposure upon glycerin bouillon.

A small quantity of the culture was inoculated under the skin of a guinea-pig, which was killed in two months and presented, at the site of inoculation, a tuberculous abscess containing Koch's bacillus, but no generalized lesions.

The authors conclude that the long sojourn in the water attenuated the virulence of the bacillus. The tables follow:

Water.	Temperature.	Addition of Bouillon Glycerin in about	Result.	Lived for
Ourcq River	20° C.	4 days.	+	
		8 "	Contaminated.	27 days.
		14 "	+	
		27 "	+	
Distilled.....	20° C.	5 "	Contaminated.	
		15 "	+	24 days.
		19 "	+	
		24 "	+	
Ourcq River	38° C.	15 "	+	
		30 "	Contaminated.	95 days.
		39 "	+	
		95 "	+	
Distilled.....	38° C.	9 "	+	
		23 "	+	
		35 "	0	115 days.
		40 "	+	
		90 "	+	
		115 "	+	
Ourcq River	35° C.	8 "	+	
		15 "	Contaminated.	
		25 "	+	30 days.
		30 "	+	
Distilled.....	35° C.	10 "	Contaminated.	
		15 "	+	
		25 "	+	27 days.
		30 "	0	

Twitchell* (1905) undertook an experiment to determine how long the tubercle bacillus would live in sputum under natural conditions. The material used was obtained by mixing in equal proportions the sputum of two patients in whom the disease was actively progressing, so as to make reasonably sure of obtaining a virulent, strongly growing organism.

The number of bacilli present in the sputums used showed from VII to VIII on Gaffky's scale.

* Twitchell, David C.: "The Vitality of Tubercle Bacilli in Sputum." Med. News, vol. lxxxvii, 1905, pp. 642–647.

The sputum from each patient was first tested by injecting 0.5 c.c. into the groins of two guinea-pigs. Ninety-one days later the first pig was killed. The pig was emaciated, and showed a large open ulcer in the right groin. Tubercle bacilli were obtained from the ulcer. The inguinal glands were enlarged and caseated, and the spleen showed tubercles. After one hundred days the second pig was killed; on autopsy it showed generalized tuberculosis.

The following are the conditions in which the sputum was placed:

First: Sputum deposited in sterilized, corked, and paraffined white glass bottles (the bottles were 3 cm. in diameter, and a depth of about 1 cm. of the mixed sputum was placed in each bottle); A, in a dark moist box; B, in a dark closet; C, in the diffuse light of an ordinary room; D, in the sunlight on glass plates (a fairly thin layer of sputum on a Petri dish); E, in the thermostat.

Second: Sputum deposited in sterilized white glass bottles stoppered with cotton; A, in dark moist box; B, in a dark closet; C, in the diffuse light of an ordinary room; D, in the thermostat.

Third: Sputum deposited in sand in sterilized white glass bottles; A, in a dark moist box; B, in a dark closet; C, in the diffuse light of an ordinary room. Bottle corked and paraffined. D, in the diffuse light of an ordinary room. Bottle not sealed. E, in the thermostat. Bottle not sealed. F, in the thermostat. Bottle corked and paraffined.

Fourth: Sputum deposited under ordinary room conditions on: A, handkerchief (folded); B, carpet; C, wood; D, woolen blanket (folded).

Fifth: Sputum deposited in the open air during the winter months in open, white glass bottles.

Sixth: Sputum deposited in sterilized white glass bottles, corked and paraffined; buried in the ground.

Seventh: Sputum deposited in sterilized white glass bottles, packed with ice, corked, and paraffined, frozen in blocks of ice.

In the experiment with sputum exposed to sunlight the specimens when not actually exposed to the sun's rays were kept in a dark box.

The experiment with the sputum placed in the sand was not satisfactory. Many pigs died early of septicemia. The sand was not sterilized, and the reclaiming of the sputum from the sand was not certain.

The experiment with sputum placed in blocks of ice was not entirely satisfactory, as it was not possible to keep the bottles frozen solid. At stated intervals the sputum, under these varying conditions, was tested by subcutaneous injection into the groins of guinea-pigs—0.25 c.c. of the sputum was injected into both groins of each guinea-pig with a glass hypodermic syringe. The site was washed with 5 per cent. carbolic acid.

One pig was inoculated with each sample of sputum to be tested. If, at the end of two or three weeks, there was no enlargement of the glands, a

second pig was inoculated with the same material. After a certain time, usually from a month to six weeks, pigs were killed. At autopsies smears from glands and tubercles were made and examined under the microscope.

The results were negative in the following instances:

With sputum in glass bottles, stoppered with cotton, placed in the diffuse light of an ordinary room (II, C), the pigs inoculated at the end of eighty-eight and a hundred days died of unknown cause a few days after the injection. With sputum in glass bottles stoppered with cotton, placed in the thermostat (II, D), no pig was inoculated between twenty-one and one hundred and one days, so that experiment was of no use as a comparison with the other specimens of that set. None of the results with the sputum in sand (III) were entirely satisfactory, owing to the death of many pigs from septic infection a few days after inoculation.

The results were negative in the case of the sputum buried (VI). The pig inoculated at the end of one hundred and two days died at the end of two weeks with no sign of tuberculosis. This inoculation could not be repeated, as the specimen was destroyed by mistake.

Summary.—(I, A) The tubercle bacilli in the sputum in paraffined bottles placed in a dark moist box were alive and produced a tuberculous lesion in a guinea-pig at the end of one hundred and seventy days. No tuberculous lesions were produced after one hundred and eighty-eight days.

(I, B) With sputum in paraffined bottles, placed in a dark closet, a lesion resulted after one hundred and sixty days, but not after one hundred and eighty-eight days.

(II, A) With the sputum in bottles stoppered with cotton, placed in a dark, moist box, a lesion resulted after one hundred and fifty-seven days, but not after one hundred and seventy-two days.

(I, C) With the sputum in paraffined bottles, placed in the diffuse lights of an ordinary room, a lesion resulted after one hundred and twenty-four days, but not after one hundred and seventy-five days.

(VII) With the sputum in ice, a lesion resulted after one hundred and two days, but not after one hundred and fifty-three days.

(III, C) With the sputum in sand, in a moist, light place, a lesion resulted after one hundred and twenty-three days, but not after one hundred and forty-eight days.

(II, B) With sputum in bottles stoppered with cotton in a dark closet, a lesion resulted after one hundred days, but not after one hundred and forty-one days.

(V) With the sputum in open bottles, placed out-of-doors in the winter months, a lesion resulted after one hundred and ten days, but not after one hundred and thirty-two days.

(IV, A) With sputum in a handkerchief, a lesion resulted after seventy days, but not after a hundred and ten days.

(IV, C) With sputum on wool, a lesion resulted after seventy days, but not after a hundred and ten days.

(I, C) With sputum in paraffined bottles, in the thermostat, a lesion resulted after thirty-three days, but not after a hundred days.

(IV, B) With sputum on carpet, a lesion resulted after thirty-nine days, but not after seventy days.

(III, D) With sputum in sand, in a dry, light place, a lesion resulted after thirty days, but not after seventy days.

(I, D) With the sputum exposed to direct sun-rays, a lesion resulted after one hour, but not after seven hours.

It appears that the conditions most conducive to the prolonged life of the tubercle bacillus in sputum are darkness and moisture. In the author's experiment, the bacilli under these conditions were alive at the end of five and a half months. Drying hastens their destruction. A temperature of about 37° C. is less favorable for them than ordinary room temperatures. A temperature near the freezing-point is less favorable for them than ordinary room temperature. The direct sun-rays kill them in a few hours.

Villemin* (1869) read a memorandum entitled "On the Propagation of Phthisis." This work contained the results of several series of experiments: (1) On the inoculation of phthisical sputum; (2) on the production of tuberculosis by means of dried phthisical sputum; (3) by the inoculation of sweat of phthisical patients; (4) on the production of tuberculosis by the ingestion of tuberculous material and phthisical sputum. Villemin used rabbits for his experiments, and all of them developed tuberculosis except those inoculated with the sweat. The author came to the following conclusions:

1. The tubercle and the material expectorated by persons with phthisis act like the virulent substances; they reproduce tuberculosis by inoculation and by absorption through the natural channels (digestion and respiration).

2. Tuberculous sputum dried several hours does not lose this property.

3. Phthisis is transmissible; its propagation takes place through the products emanating from the sick individuals.

Zilgien† (1890), in his doctoral thesis, states that Feltz, in former experiments upon the resistance of the tubercle bacillus, mixed it with the dust of roads. At varying times some of this dust was inoculated into guinea-pigs by making a little subcutaneous incision, into which some of the tuberculous dust was deposited, having first been moistened with distilled water. The

* Villemin: "De la propagation de la phthisie," Mem. acad. de med., Paris, vol. xxxiv, 1869, p. 242.

† Zilgien, Henri: "Essai expérimental et clinique sur le rôle des poussières bacillaires dans la contagion de la tuberculose et sur la durée de la virulence de ces poussières." Thèse pour le Doctorat en Médecine, Faculté de Médecine de Nancy, December 26, 1890. Disserta. da la Fac. Méd. de Nancy, vol. xxxi, 314–324, 1890–91.

dust was exposed at the different temperatures (30° to 70° C.) for three months, and inoculations made from month to month, with the following results:

Inoculated 5 Guinea-pigs on—	40° C.	50° C.	60° C.	70° C.
July 28, 1889...	All dead of tuberculosis in 4 months.	All dead of tuberculosis in 4 months.	Three died of tuberculosis; 2 remained well.	None died.
Aug. 29.....	Three died in 4 to 5 months.	Three died in 3 to 4 months.	One died; 4 remained well.	None died.
Sept. 29.....	One died; 2 remained well.	Three died in 3 to 4 months; 2 remained well.	One died; 4 remained well.	None died.
Oct. 30.....	One died after 4 months.	None died.	None died.	None died.
Nov. 14.....	One died after 3 months.	None died.	None died.	None died.

In another series of experiments Feltz, with the assistance of Zilgien, dried sputum rich in bacilli at 75° C. for forty-eight hours. Guinea-pigs were inoculated, but none of them showed any trace of tuberculosis.

A third series of experiments was done by Feltz by mixing road dust with fresh tuberculous expectoration, which showed, on microscopical examination, a large number of Koch's bacilli. The mixture so obtained was divided into three parts. The first part was exposed to the sun, the second placed in the incubator at 40° C., and the third dried in the sun and then exposed to the weather in a box the cover of which was perforated with many holes.

Exposed to the Sun.	Kept in the Incubator at 40° C.	Exposed to the Weather.
Sept. 15, 1887: Inoculated 12 guinea-pigs. All died of tuberculosis Jan. to March, 1888.	Sept. 15, 1887: Inoculated 12 guinea-pigs. All died of tuberculosis Dec. to Feb.	Dec. 3, 1887: Inoculated 12 guinea-pigs; 4 died of tuberculosis in 6 months; the rest remained well.
Jan. 2 (mixture 46 days old): 10 pigs inoculated; 3 died Jan. to May; 7 remained well.	Apr. 4: 10 pigs inoculated; 2 died about May; 8 remained well.	Feb. 10: 10 pigs inoculated. All 10 remained well.
Apr. 4 (137 days): 8 pigs inoculated; 1 died June 4; 7 remained well.	July 1: 8 pigs inoculated; 2 died about August; rest remained well.	July 1: 10 pigs inoculated. Following Jan. none had died, all well.
July 1 (227 days): 10 pigs inoculated. Jan., none dead or sick.	July 1: 6 pigs inoculated. Jan., none dead or sick.	....

The conclusion is drawn that the tubercle bacillus lives a very long time in dust exposed to the weather—somewhat over seven months; about one hundred and forty days when exposed to the sun. Further experiments demonstrated that sputum dried in rooms preserves its virulence till the seventh or ninth month.

THE ACTION OF DIFFUSE LIGHT UPON BACILLUS TUBERCULOSIS.

By John Weinzirl, Ph.D.,

Bacteriological Laboratory, University of Washington, Seattle, Washington.

The action of direct sunlight upon bacteria has been the subject of numerous investigations; the results, however, were obtained by unsatisfactory methods and greatly minimize the effect of this important hygienic factor. In the earlier investigations cultures were made in various media, usually agar, and these cultures were exposed to sunlight. By this method sufficient light was absorbed by the medium so that the time required to kill the bacteria was prolonged ten or twenty times. By making direct exposure, *i. e.*, without the intervention of media, the writer has recently shown* that non-spore-bearing bacteria, including B. tuberculosis, are killed by direct sunlight in a remarkably short time, generally between two and ten minutes.

As to the effect of diffuse light we have most meager data, and these were obtained by the older method. It appeared desirable to take advantage of the new method to test likewise the action of diffuse light, especially upon B. tuberculosis.

That diffuse light is an important hygienic factor is generally assumed, and the construction of barns, factories, stores, and more especially dwellings, is usually planned with this point in view. Buchner's result with B. typhosus, which he found was killed by five hours of exposure to diffuse light, would tend to confirm this assumption. Koch exposed cultures of B. tuberculosis near a window and found that they were killed in five to seven days. This result was also regarded as indicating the importance of diffuse light. Koch, furthermore, seems to have regarded B. tuberculosis as unusually sensitive to light-action.

If, then, the question is raised whether it is desirable to materially increase the window surface, and hence the amount of both direct and diffuse light in our dwellings, so that the chances of infection from tuberculosis and other

* Journal of Infectious Diseases, 1907.

diseases may be lessened, we appreciate the need of more data. The present investigation was undertaken with this question in mind.

The Method of Exposure.

In estimating the value of results, it is essential to know how those results were obtained. In the present investigation the same method was employed as in the writer's earlier work on the action of direct sunlight already referred to. The bacterial cultures were inoculated into sterile normal salt solution and shaken to give a homogeneous suspension. A loopful of this suspension was then inoculated upon sterile slips of paper placed in petri dishes. The long exposures made it necessary to place the covers on the dishes and to allow the diffuse light to pass through the glass covers; however, no medium was employed, and this obviated the most serious objection to the earlier investigations. After exposing the inoculated papers for a given time, they were placed in or on a suitable medium and incubated. For most bacteria, bouillon served very well, but for B. tuberculosis Dorset's egg medium, freshly moistened with water or bouillon, was invariably used. By this method B. tuberculosis has been found to grow well upon the paper slips.

The exposures were made in a laboratory which received all its light from east windows. The shades were kept about two-thirds rolled up, although this was not invariably the case. The petri plates containing the inoculated papers were placed on the top of a cupboard twelve feet from the windows, where direct sunlight could not strike them at any time. These conditions were assumed as an average of what might obtain in dwellings, although, of course, the latter vary within wide limits. The papers were left exposed continually until placed in a medium and incubated. Controls kept in the dark were invariably made, and at times other controls were placed in glass desiccators and moist chambers, both being exposed to the light.

Results of Exposure to Diffuse Light.

(A) *Action on Bacteria in General.*—On account of the slow growth of B. tuberculosis, and also for purposes of comparison, a number of tests were made with some of the common laboratory forms; these may be tabulated, for convenience, as follows:

TABLE I.—SHOWING RESULTS OF EXPOSING BACTERIA TO DIFFUSE LIGHT.

Organism.	Date.	Conditions.	Result of Exposure (Days).	
			Growth.	No Growth.
Str. erysipelatis	Apr. 10.	Diffuse light.	1, 2, 3, 4.	....
"	"	Dark control.	1, 2, 3, 4.	....
"	"	Moist control.	1, 2.	3, 4.
"	May 16.	Diffuse light.	5.	6, 8, 10.
"	"	Dark control.	5, 6, 8, 10, 12.	14.
"	"	Moist control.	5, 6, 8.	....
"	May 30.	Diffuse light.	4, 5.	6, 7, 8.
"	"	Dark control.	8.	....
"	"	Moist control.	1, 2, 3, 4.	5, 6.
"	June 11.	Diffuse light.	3, 4, 5, 7.	9, 11.
"	"	Dark control.	4, 7.	....
"	"	Moist control.	1, 3.	4, 5, 7, 9.
"	"	Dry control.	1, 3, 4, 5, 7, 9.	....
"	July 9.	Moist control.	....	1, 2, 4.
"	"	Dry control.	1, 2, 4.	11, 14.
Staph. pyogenes albus	Apr. 4.	Diffuse light.	4, 5, 6, 7.	8, 10.
"	"	Dark control.	4, 5, 6, 7, 8, 10.	....
"	"	Moist control.	....	4, 5, 6, 7, 8, 10.
"	July 9.	Diffuse light.	1, 2, 4, 7.	11.
"	"	Dark control.	1, 2, 4, 7.	11.
"	"	Moist control.	1, 2.	4, 7, 11.
B. prodigiosus	June 28.	Diffuse light.	....	1, 3, 4, 5, 6.
"	"	Dark control.	1, 3, 4, 5.	6.
"	"	Moist control.	....	1, 3, 4, 5, 6.
"	July 5.	Diffuse light.	....	1, 2, 4.
"	"	Dark control.	1, 2, 3, 5.	8.
"	"	Moist control.	....	1, 2, 3, 4.
B. coli	Mar. 6.	Diffuse light.	5 (hrs.).	8, 24 (hrs.).
"	"	Dark control.	5, 24 (hrs.).	8 (hrs.).
"	Mar. 21.	Diffuse light.	....	7, 23, 31 (hrs.).
"	"	Dark control.	7 (hrs.).	23, 31 (hrs.).
"	"	Moist control.	7, 23 (hrs.).	31 (hrs.).

From these trials, it appears that Str. erysipelatis and Staph. pyogenes albus possess considerable resistance to diffuse light, the average length of time required to kill being about seven days. On the other hand, B. coli and B. prodigiosus were killed within a day; in one instance B. coli was killed within seven hours, while in the other it was not killed in five hours of exposure. The data show very plainly that many more organisms must be worked before accurate conclusions can be drawn with respect to the bacteria in general. This becomes especially evident when an attempt is made to estimate the relative part played by disturbing factors.

The effect of desiccation was supposed to be the most serious disturbing factor, and, hence, controls in moist chambers were also exposed to diffuse light. Similar controls placed in desiccators were occasionally run, as an additional check; the moist controls were killed before the desiccated ones, and, also, before the cultures controlled. It will be necessary to place

similar cultures in the dark before the true import of these factors can be determined. The present inference is that moisture promotes the germicidal effect of diffuse light. This part of the problem is still under investigation.

(B) *Action on B. tuberculosis.*—The results for B. tuberculosis are tabulated as follows:

TABLE II.—SHOWING RESULTS OF EXPOSING B. TUBERCULOSIS TO DIFFUSE LIGHT.

Organism.	Date.	Conditions.	Result of Exposure (Days).	
			Growth.	No Growth
B. tuberculosis.....	Mar. 3.	Diffuse light.	1, 3.	5, 7, 10.
"	"	Dark control.	1, 3, 5, 7.	10.
"	May 2.	Diffuse light.	2.	3, 4, 5, 7, 10.
"	"	Dark control.	2, 3, 4, 5.	7, 10.
"	May 16.	Diffuse light.	....	5, 6, 8, 10, 12.
"	"	Dark control.	5, 6.	8, 10, 12.
"	May 31.	Diffuse light.	1, 3.	6, 9.
"	"	Dark control.	1, 3, 6.	9.
"	June 10.	Diffuse light.	....	1, 2, 4, 6, 8.
"	"	Dark control.	1, 4.	2, 8, 10.
"	July 2.	Diffuse light.	1, 2.	4, 5.
"	"	Dark control.	1, 2.	5.
"	"	Moist control.	1.	2, 4, 5.
"	"	Dry control.	1.	4, 5.
"	July 10.	Diffuse light.	....	1, 2, 4, 6, 8.
"	"	Dark control.	1, 2, 4.	8.
"	"	Moist control.	1, 4.	2, 6.
"	July 26.	Diffuse light.	1, 3, 5.	8, 10.
"	"	Dark control.	1, 3, 5, 8.	....
"	"	Moist control.	1, 3, 5, 8, 10.	....
"	"	Dry control.	1, 3.	5, 8, 10.
"	"	Diffuse light.	1, 3.	5, 8, 10.
"	"	Dark control.	1, 3, 5, 8.	10.
"	"	Moist control.	....	1, 3, 5, 8, 10.
"	"	Dry control.	1.	3, 5, 8, 10.
"	"	Diffuse light.	1, 3, 5, 10.	8.
"	"	Dark control.	1, 3, 5, 8, 10.	....
"	"	Moist control.	1, 3, 5.	8.
"	"	Dry control.	1, 3, 5, 10.	8.

In the above trials, three cultures of B. tuberculosis were used, two human and one avian. The results indicate no important differences between them when exposed to diffuse light.

Considerable variation is shown in the different trials made. The shortest time required to kill was less than twenty-four hours, and the longest time was ten days. The considerable variation is not at all surprising when the various disturbing factors are considered. These factors are: (*a*) The amount of diffuse light varies within wide limits, depending upon the amount of sunshine. (*b*) The suspensions of bacteria are apt to vary widely in density. (*c*) Desiccation alone will kill the bacteria, and may play a con-

siderable rôle here. (*d*) As the results already considered have shown, the presence of moisture appears to hasten the germicidal action of diffuse light. (*e*) The age of culture used may also vary the result.

Remembering that in nature the conditions must vary much more widely still, the results may be considered sufficiently accurate for present purposes.

Controls kept in the dark lived longer than the cultures exposed; but these, too, were killed in a comparatively short time. This phenomenon was unexpected and led to the making of still other controls; for this purpose similar cultures were placed in glass vessels, one filled with concentrated sulphuric acid and the other with water; the former would contain practically dry air, while the latter was saturated at all times with water vapor. Only five experiments on B. tuberculosis are completed, and the results are far from being harmonious.

Conclusion.

These experiments not only confirm the view that diffuse light acts as a germicidal agent, but they also show that such light possesses a true germicidal effect independent of desiccation. Specifically, they show that B. tuberculosis is killed by diffuse light within a week, usually within three or four days, and it may be killed even within a single day. It is, however, not as sensitive as some of the other bacteria.

VERGLEICHENDE UNTERSUCHUNGEN ÜBER DIE PRAKTISCH WICHTIGSTEN SÄUREFESTEN BACILLEN.

Dr. N. Jancso und Dr. A. Elfer.

Aus der Medizinischen Klinik der Universität in Kolozsvar. (Direktor Prof. Dr. Purjetz.)

Unsere Untersuchungen beziehen sich auf Kulturen, die aus 93 tuberkulösen Menschen, 11 Rindern, 1 Schwein, 18 Hühnern gezüchtet wurden, und zwar zum grössten Teil direkt auf Nährboden; unsere Beobachtungen sind das Resultat von an 10 Kälbern, 14 Ziegen, mehr als 1200 Kaninchen, und mehr als 400 Meerschweinchen, 300 Hühnern, 500 Fröschen, 31 Schlangen vorgenommenen Untersuchungen.

Wir fassen unsere Beobachtungen zusammen wie folgt:

1. Hinsichtlich ihrer wesentlichen Eigenschaften lassen sich unsere sämtlichen Kulturen in drei bezüglich ihrer morphologischen Verhältnisse und ihrer Pathogenität ziemlich scharf unterscheidbare Kulturgruppen einteilen, welche dem Typus humanus, dem Typus bovinus, und dem Typus aviarius entsprechen.

2. Unsere aus 11 Rindern gezüchteten Stämme erwiesen sich alle als Typus bovinus.

3. Unsere aus 18 Hühnern gezüchteten Stämme erwiesen sich alle als Typus aviarius.

4. Der aus einem Schwein gezüchtete Stamm entsprach dem Typus bovinus.

5. Unter den von uns aus 93 tuberkulösen Menschen gezüchteten Stämmen kommt einer vor, der seinen sämtlichen kennzeichnenden Eigenschaften nach unter gewöhnlichen Verhältnissen zu den in andern Organismen lebenden Stämmen zu rechnen ist: der Typus aviarius. Demzufolge können wir behaupten, dass unter den aus Menschen zu gewinnenden Stämmen auch solche vorkommen, welche ihren sämtlichen kennzeichnenden Eigenschaften nach dieselben sind wie die unter gewöhnlichen Verhältnissen in andern Organismen—Rindern, Hühnern—lebenden säurefesten Stämme; obzwar wir unter den aus 93 tuberkulösen Menschen gezüchteten Stämmen, deren 22 aus Menschen unter 14 Jahren stammen, keinen einzigen gefunden haben, welcher seiner Zuchteigenschaften, sowie seiner in Kaninchen und grösseren Tieren erwiesenen Pathogenität halber zum Typus bovinus gerechnet werden könnte.

6. Aus unseren vergleichenden Untersuchungen mit streng zu einer Gruppe gehörigen Tuberkelstämmen ergibt sich, dass streng zu ein und derselben Gruppe gehörige Tuberkelstämme in ihren inneren Eigenschaften, in ihrer Virulenz doch von einander abweichen können.

7. Obwohl genau genommen die menschlichen Stämme zum grössten Teil in Kaninchen nur unbedeutende tuberkulöse Veränderungen hervorbringen, haben wir unter ihnen doch auch solche gefunden, welche auf das Kaninchen tötlich wirkten; diesen Umstand demonstrieren wir in der Weise, dass wir die Versuchstiere längere Zeit am Leben erhalten, d. h., dass wir bei den Bacillen die Dauerzeit ihrer Lebenstätigkeit nicht abkürzen.

8. Die aus verschiedenen Organen ein und desselben tuberkulösen Individuums gezüchteten Stämme zeigen untereinander auffallende Verschiedenheiten in Bezug auf ihre wesentlichen Eigenschaften.

Versuche zur Erreichung von Eigenschaftsveränderungen bei menschlichem Tuberkelbacillus.

(*a*) Unsere Versuche über die Modificationen, welche sich in der Reinkultur der menschlichen Tuberkelstämme erreichen lassen, haben bis jetzt noch keine derartige Daten ergeben, dass die Verminderung einer sonst specifisch zu nennenden Eigenschaft aufgewiesen hätte; noch konnten wir im Laufe unserer Experimente den Versuchsstämmen solche fundamentale Eigenschaften geben, welche bei diesen Stämmen in steigendem und immer stärkerem Masse zu wesentlichen, bis functionellen Eigenschaften geworden wären.

(*b*) Auf Grund unserer mit 16 Stämmen vorgenommenen zahlreichen Versuche müssen wir sagen: es ist uns in 2–3 Jahren nicht gelungen, mittels Kaninchenpassagen die pathogene Wirkung des Typ. humanus auf Kaninchen soweit zu modificieren, dass sich diese Eigenschaft wenigstens eine gewisse Zeit hindurch in gesteigertem Masse gezeigt hätte, und besonders konnten wir keine derartige Veränderungen erzielen, wie sie die Stämme des nicht modificierten Typus bovinus gewöhnlich zeigen, ob wir nur die Stämme wiederholt durch den Kaninchenkörper geführt (VII–IX Passagen) oder dieselben längere Zeit im Körper des Tieres gelassen haben.

(*c*) Bei den an grösseren Säugetieren vorgenommenen Passagen sehen wir, dass wir bis jetzt von keinem Fall berichten können, wo unsere Stämme menschlicher Tuberkulose bei Inanspruchnahme grösserer Tiere eine innerliche modificierte Pathogenität in Bezug auf Kaninchen gezeigt hätten; andererseits haben wir beobachtet, dass die stufenweisen Tierpassagen (Kaninchen, Ziege, Kalb) imstande sind, die in der ursprünglichen Stammzucht latent vorhandenen Eigenschaften elektiv zu steigern, so dass die anfängliche pathogene Wirkung denselben Tieren gegenüber sich in bedeutend stärkerem Masse zeigt, und scheinbar auch eine Modification der Patho-

genität imitieren kann. Wir sind geneigt auch die verschiedenen Erscheinungen der sogenannten "atypischen" "Übergangsstämme," sowie die durch die Tierpassagen erreichbare sogenannte Virulenzsteigerung auf die starke Anziehung zurück zu führen, welche vielleicht irgend ein ausscheidender äusserer Faktor auf eine solche latente Eigenschaft ausübt. Ob nun diese zutage gekommene verstärkte Eigenschaft den wirklichen Stämmen der ursprünglichen Stammkultur spezifisch ist, weil durch irgendwelche Umstände sehr nahverwandte, aber dennoch andere innere Eigenschaften aufweisende Stämme hingelangt sind, darüber können wir uns auf Grund unserer bisherigen Erfahrungen nicht äussern.

(*d*) Mit den menschlichen Tuberkelstämmen können wir in Hühnern eine lokale tuberkulöse Veränderung hervorrufen, sowohl mit subcutaner, als mit Bauchhöhleninfection. Mit intravenöser Infection haben wir in den inneren Organen die von denselben Tuberkelstämmen erwarteten Tuberkeln selbst bei Kontrolle mit Reinkulturen nicht bemerkt. Ebensowenig haben wir bei subcutaner Infection trotz der ziemlich starken Infectionsdosis in den inneren Organen keine Entstehung von Tuberkeln beobachtet.

Bei den auf Nocard's Untersuchungen begründeten Modifizierungsversuchen, die wir an sechs menschlichen Stammkulturen vorgenommen, ist es uns in keinem einzigen Fall gelungen, trotz genauer Kontrolle mit Reinkulturen an denselben die Eigenschaften des Typus gallinaceus zu entdecken (es ist wahr, dass wir keine mehrfachen Passagen vorgenommen haben).

(*c*) Unsere Versuche mit niedrigeren Reptilien—Schlangen, Fröschen—bei denen wir die Reinkulturen möglichst unmittelbar gewannen, beweisen einheitlich, im Anschluss an vergleichende Versuche, dass es uns nicht gelungen ist, mit Stämmen von Tuberkelbacillen aus Menschen Veränderungen in Reptilien hervorzurufen; innerhalb der Zeit dieser Versuche sind wir nicht imstande gewesen, die Stammkulturen mit einer solchen dauernden Eigenschaft zu versehen, welche sie im nicht modificierten Zustand entbehren. Die in den Kaltblütern am Leben gebliebenen menschlichen Tuberkelstämme haben gewisse ziemlich innerliche Eigenschaften mit Fähigkeit festgehalten, unter welchen wir vor allen ihre äussere Gestalt auf künstlichem Nährboden, ihre Anpassungsverhältnisse an äussere Temperatur und ihre unveränderte pathogene Wirkung auf Meerschweinchen hervorheben.

Versuche zur Veränderung der Eigenschaften in aus Rindern gezüchteten Stämmen.

(*a*) In Bezug auf die durch Reinkulturen erreichbaren Modificationen bei diesen Stämmen können wir dasselbe sagen, wie bei den menschlichen Tuberkelbacillenstämmen.

(*b*) Vier Versuche, die wir mit einem Stamm des Typus bovinus an

Hühnern gemacht haben, beweisen, dass die kürzere oder längere Zeit in den Hühnern lebenden Stämme des Typus bovinus sich weder in ihren Kultureigenschaften, noch in ihrer Pathogenität den Kaninchen gegenüber wesentlich verändert haben, höchstens dass ihre pathogene Wirkung in Kaninchen mehr oder minder verringert ward. Aber selbst die Stämme, deren Pathogenität in bedeutendem Masse verringert war, behielten dennoch ihre charakteristische Pathogenität bei.

Aus den in der Bauchhöhle der Hühner in Collodiumsäckchen untergebrachten Stämmen des Typus bovinus konnten wir in zwei Fällen nach 257 resp. 278 Tagen Reinkulturen gewinnen, welche sich von den Original-Stammkulturen bloss durch ihr üppigeres Wachsen unterscheiden. Geflügel, welche mit den in den Hühnern kürzere oder längere Zeit verweilenden Bacillenmassen, oder mit den aus diesen gezüchteten Reinkulturen geimpft wurden, zeigten in keinem einzigen Falle generalisierte Tuberkulose.

(*c*) Unsere mit vier Stämmen an Reptilien gemachten Versuche haben gezeigt, dass es uns im Laufe von zwei Jahren nicht gelungen ist, die wesentlichen Stammeigenschaften des Typus bovinus bedeutend zu verändern; auch konnten wir keine Annäherung desselben an die übrigen Typen, ebensowenig an die Frosch- oder Fischtuberkulose erzielen.

Versuche zur Veränderung der Eigenschaften im Typus Gallinaceus.

(*a*) In Bezug auf erreichbare Modification durch Reinkultur sind unsere Beobachtungen dieselben, wie bei den Stämmen des Typus humanus.

(*b*) Einer unserer Stämme des Typus gallinaceus während und nach seiner 60Stägigen Kaninchen- und Meerschweinchenpassage, zwei andere unserer Stämme während und nach ihrer 264, relativ 313tägigen Kaninchen- und Meerschweinchenpassage haben in Reinkulturen keine Modificationen gezeigt. In Meerschweinchen haben diese Stämme keine gesteigerten Veränderungen hervorgerufen, ihre Pathogenität gegenüber den Hühnern war auch gar nicht abgeschwächt.

(*c*) Reptilienpassagen mit zwei Stämmen des Typus gallinaceus aus Hühnern, und ein Stamm des Typus gallinaceus aus Menschen haben gezeigt, dass uns nicht gelungen ist, durch dieselben tuberkulöse Veränderungen in Reptilien hervorzurufen, und dass wir in den uns zu Verfügung stehenden 2–3 Jahren nicht imstande gewesen sind, die Stämme derart zu verändern, dass sie dadurch eine Annäherung an andere säurefeste Stämme gezeigt hätten und ebensowenig an Frosch- und Fischtuberkulose.

Die Wichtigkeit einer unmittelbaren gegenseitigen Aufeinanderwirkung der verschiedenen säurefesten Stämme.

Unser Ziel bei diesen Versuchen war nicht die von den gemischten Stämmen entwickelten Veränderungen, sowie die morphologischen Ver-

hältnisse ihrer auf künstlichen Nährboden zutage tretenden gegenseitigen Entwickelungsfähigkeit zu beobachten, sondern die gewisse Zeitlang unter gewissen Umständen sich mit einander entwickelnden verschiedenen säurefesten Bacillen getrennt zu untersuchen ob etwa ein säurefester Stamm einige Annäherung zu einem anderen zeige. Diese unsere Untersuchungen haben erwiesen, dass nicht nur solche Kulturen auch andere Arten von säurefesten Stämmen in sich bergen können, welche äusserlich als absolute Reinkulturen erscheinen, sondern dass auch die gänzlich isolierten, scheinbar aus einzigem Bacillus auswachsenden kleinsten Kulturen eine Mischung von säurefesten Bacillen verschiedener Typen bergen können, was bei einfacher Besichtigung unmöglich zu erkennen ist, nur unter dem Mikroscop und mittels Tierversuche.

* * * *

Unsere Untersuchungen über die Modificationen der verschiedenen säurefesten Stämme haben also gezeigt, wie verhältnismässig leicht bei den verschiedenen säurefesten Gruppen ihre unter ihren gegenwärtigen Lebensverhältnissen erworbenen Eigenschaften und unter diesen hauptsächlich ihre specifische Pathogenität abzustumpfen ist, und demnach ist vorauszusetzen, dass die verschiedenen säurefesten Stämme dieser specifischen Eigenschaften auch gänzlich beraubt werden können.

Wie leicht es jedoch auch sein mag bei einzelnen säurefesten Stämmen irgend eine sich äusserlich kundgebende Eigenschaft abzustumpfen—vielleicht auch sie ihnen ganz zu nehmen—so ausserordentlich schwer ist die Übertragung von neuen specifischen Eigenschaften, so dass sie im streng naturwissenschaftlichen Sinne bisher noch keinem einzigen Forscher gelungen ist. Solange uns keine sicheren, mit angewandter Reinkulturenkontrolle vorgenommenen, überzeugungskräftigen Transformationsversuche zu Verfügung stehen, werden Untersuchungen mit solchen Endresultaten wie die unsrigen stets nur beweisen, dass unter den heutigen Lebensumständen die wichtigeren Gruppen der säurefesten Bacillen sich im Haushalte der Natur mehr und mehr von einander entfernen.

Concerning the Practically Important Acid-fast Bacilli.—(JANSCO AND ELFER.)

Conclusions.—Cultures were made from 93 tuberculous patients, 11 bovines, 1 pig, and 18 chickens; for the greater part, the inoculations were made directly on nutritive media, and, for further study, were employed 10 calves, 14 goats, more than 1200 rabbits, more than 400 guinea-pigs,

300 chickens, 300 frogs, and 31 snakes. The following results were obtained:

1. In relation to their main characteristics, their morphology and pathogenesis, all the cultures could be divided rather sharply into three groups; they corresponded to the typus humanus, bovinus, and aviarius.

2. All the cultures cultivated from the 11 bovines were found to belong to the typus bovinus.

3. The strains cultivated from the 18 chickens were all found to belong to the typus aviarius.

4. The strain from the pig belonged to the typus bovinus.

5. Among the strains cultivated from the 93 tuberculous patients, there was one with all the characteristic properties which, under ordinary conditions, are found only in strains living in other organisms: the typus aviarius. It may therefore be asserted that, among the strains developed from the excreta of human beings, there are also to be found some which, according to all their characteristic properties, are the same living acid-fast bacteria as occur under ordinary conditions in other animals—bovines, chickens; this is probably true, even though the authors were not able to isolate a single strain from among the 93 tuberculous patients (22 of whom were individuals younger than fourteen), which because of its characteristics of cultivation, as well as because of its pathogenicity toward rabbits and larger animals, could be counted as belonging to the bovine type.

6. From comparative studies made by the authors with tubercle bacilli belonging to the same group, they were able to show that such organisms, even though belonging to absolutely one and the same group, may vary from each other in many of their characteristics, in their virulence, etc.

7. On the whole, most of the human strains produce but slight tuberculous changes in rabbits; several exceptions, however, have been found by the authors, in which the organisms produced a fatal termination in the rabbits; this fact the authors have demonstrated in this manner: They have kept the animals which were being experimented on alive for some time, and have thus not shortened the duration of vital activity of the bacilli.

8. Organisms cultivated from different organs of one and the same individual show marked variations from the standpoint of their most important characteristics.

9. The investigations of the authors have shown how relatively easy it is to lessen the characteristics acquired by the different acid-fast groups in their present mode of life, and among these more particularly

their specific pathogenicity; it is, therefore, to be assumed that the various acid-fast strains could be deprived entirely of their specific properties.

10. However easy it may be to weaken some characteristics of individual acid-fast strains, and even to remove them entirely, it is extraordinarily difficult to confer upon them new specific properties; no investigator has, in fact, ever succeeded in a manner satisfactory to the laws of natural science. As long as we have not at our disposal certain incontrovertible transformation experiments performed and controlled with pure cultures, examinations with such terminal results as those of the authors will prove only that under the present modes of life the more important groups of acid-fast bacilli become more and more separated from each other in the realm of nature.

EIN BEITRAG ZUR KENNTNIS DER KULTURELLEN EIGENSCHAFTEN DER TUBERKELBACILLEN.

VON DR. JOHANN VON SZABOKY,
Budapest-Gleichenberg.

Aus den in dieser Arbeit angeführten Untersuchungen ist zu ersehen:

1. Dass die Ueppigkeit des Wachstums der Tuberkelbacillen auf verschiedenen Nährböden verschieden ist. Am besten wuchsen sie auf Lungenagar, dann auf Sputumagar, Sputumlungenagar, tuberk. Lungenagar; weniger gut auf Eiernährböden und auf Somatoseagar.

2. Die Tuberkelbacillen entwickelten sich am besten und schnellsten auf den ganz schwach sauren, ziemlich gut auf den schwach sauren, neutralen und alkalischen, schlecht aber auf den stark sauren Nährböden. Eine Ausnahme machte der Somatoseagar und der Eiernährboden. Auf ersterem gediehen sie am besten und schnellsten auf den stark alkalischen, schlechter auf schwach alkalischen, und am schlechtesten auf den sauren Nährböden. Auf Eiernährböden wuchsen die Kulturen auf dem stark sauren am besten, weniger gut auf den stark alkalischen, schwach auf dem neutralen Boden.

Bei diesen Untersuchungen halte ich einen Zufall für ausgeschlossen, da bei den meisten Kulturen die Schnelligkeit ihrer Entwickelung mit der Ueppigkeit der Vegetation harmonierte.

3. Das Wachstum war stets auf den feuchtesten Nährböden am üppigsten, z. B. auf Lungenagar, am schlechtesten auf Eiernährboden, welcher die wenigste Feuchtigkeit besass.

4. Es ist anzunehmen, da durch Titrierung zu ersehen war, dass die Reaktionen neutral angelegter Nährböden nach mehrtägigem Gedeihen der Kulturen verschieden waren, dass die Tuberkelbacillen durch ihre Vegetation einen Umschlag der ursprünglichen Reaktion des Nährsubstrates bewirkten. Ein solcher Umschlag erfolgte in jeder Versuchsreihe zweimal: bei allen titrierbaren Nährböden, mit Ausnahme des Somatoseagars, in der Weise, dass anfänglich alkalische, dann saure, und endlich wieder alkalische Reaktion auftrat. Bei Somatoseagar war das Umgekehrte zu konstatieren.

Cultural Characteristics of Tubercle Bacillus.—(VON SZABOKY.)

The experiments performed by the author gave the following results:

1. The luxuriance of growth of tubercle bacilli varies according to the

nutritive medium employed. They thrive best on lung-agar, next on sputum-agar, sputum-lung-agar, tuberculous lung-agar; not so well on egg-media and somatose-agar.

2. The tubercle bacilli grew best and quickest on the very weak acid media, fairly well on the slightly weak acid, neutral, and alkaline media, and not well on the markedly acid media. Exceptions to this are somatose-agar and egg-media. On the former, they thrived best and quickest when the agar was markedly alkaline, next when it was weakly alkaline, and worst when it was acid. When egg-media were employed, the best cultures were obtained when the reaction was markedly acid, next when it was markedly alkaline, and least when it was neutral.

As in the greater number of cultures the rapidity of their development corresponded with the luxuriance of the vegetation, accidental results must be considered excluded in these experiments.

3. The growth was constantly the best on media which were very moist, as lung-agar; worst on egg-media, which possesses the least moisture.

4. It is to be supposed that the tubercle bacilli produce a change of the original reaction of the nutritive medium during their growth, as titration has demonstrated that the reaction of neutral media had changed somewhat after the cultures had grown for several days. Such a change of reaction was noted in each series twice. In all the media which could be titrated, with the exception of the somatose-agar, the following change was noted: First alkaline, then acid, and finally again alkaline reaction was noticed; in somatose-agar the reverse order was noted.

NOUVELLES CULTURES HOMOGÈNES DU BACILLE DE LA TUBERCULOSE.

PAR MM. S. ARLOING ET PAUL COURMONT,
de Lyon.

Depuis dix ans, nous étudions a Lyon les "cultures homogènes du bacille de la tuberculose." Nous en possédons actuellement sept échantillons: quatre *d'origine humaine*, une *bovine* et deux *aviaires*. Une longue expérience nous permet actuellement de comparer les caractères de ces différentes cultures, dont la plus ancienne, la culture A (Arloing) a été la plus étudiée.

I. HISTORIQUE.

C'est en 1898 que M. Arloing découvrit la première de ces cultures homogènes[1]. Quelques temps auparavant Ferran (de Barcelone) avait déjà obtenu une culture homogène et étudié certains de ses caractères; mais son travail avait passé inaperçu en France a ce moment[2]. Dès 1898 nous étudiames les meilleurs moyens "pour obtenir les cultures homogènes du B. de Koch les plus propices à l'agglutination[3];" puis, dans divers mémoires, de 1898 à 1902, nous avons exposé, les diverses propriétés de ces cultures. Le caractère homogène, les caractères de végétabilité, de virulence, de morphologie extérieure, de mobilité, de colorabilité, etc., furent ainsi exposés dans des travaux faits, soit dans un but purement théorique[4], soit en vue du séro-diagnostic de la tuberculose[5]. De nombreux auteurs a cette époque suivirent notre technique et etudièrent ces cultures, principalement au point de vue de l'agglutination[6]; ils cultivèrent ainsi notre bacille A que nous leur avions envoyé; quelques-uns (Ferré, Mongour et Buard) obtenerent de leur coté des cultures homogènes provenant d'autres sources.

Paul Courmont étendit en 1902 la méthode des cultures homogènes à tous les autres bacilles acido-résistants (avec Descos)[7] et publia en 1903 la description d'un agitateur électrique pour homogénéiser les cultures dans la chambre étuve[8]. La même année il étudia avec Potet, les rapports entre les bacilles acido-résistants et le B. de Koch en cultures homogènes[20].

Toujours en 1903 Auclaire[10] fait une bonne étude sur les cultures homogènes du B. de Koch, confirmant nos travaux et les complétant sur certains points; Ferran[10] revient sur ses recherches antérieures, et Hawthorn[12] fait connaitre quelques détails interessants.

En 1904, Paul Courmont et Nicolas cultivent le bacille aviaire en cultures homogènes[13], et S. Arloing et P. Courmont publient deux articles successifs sur les différences d'agglutinabilité de six cultures homogènes de diverses origines[14].

En 1905, Rosenberger publie une note sur les cultures homogènes.[15]

II. Origine, Obtention et entretien des cultures homogènes.

L'un de nous a publié les détails du procédé employé pour obtenir sa première culture homogène d'origine humaine[1]. Depuis lors nous en avons obtenu six autres: trois autres d'origine humaine, deux d'origine aviaire, une d'origine bovine. Ces faits et les observations des autres auteurs montrent que ce n'est pas seulement par exception que le bacille de Koch pousse a l'état homogène en bouillon. Les cultures anciennes, c'est a dire entretenues depuis longtemps en laboratoire sur les milieux usuels semblant les plus faciles a adapter a l'état homogène, surtout lorsqu'elles ont acquis spontanément cet aspect gras et humide qui les fait souvent ressembler aux cultures aviaires alors même qu'elles sont d'origine humaine. C'est ainsi que P. Courmont en 1905 a pu facilement, en quelques semaines, faire pousser en cultures homogènes le premier bacille humain isolé par Koch lui même (x) et entretenu en laboratoire sur milieux usuels depuis vingt-six ans. Mais d'autre part, une culture d'origine humaine (crachats) isolée du cobaye depuis quelques mois a peine par M. Heymans (de Gand) et remise en 1901 à P. Courmont a pu être homogénéisée presque aussi facilement et rapidement. D'autres cultures humaines au contraire ont été traitées de la même façon pendant plusieurs années sans pouvoir se cultiver a l'état homogène; c'etaient des cultures conservant indéfiniment l'aspect sec et écailleux classique sur milieux solides.

Les cultures homogènes ne le sont pas complètement dès les premières générations; ce n'est que par des transplantations rapides, successives et nombreuses que l'on obtient une adaptation parfaite.

L'agitation journalière, ou plusieurs fois par jour, du ballon de culture est une condition indispensable (au début tout au moins) de l'entretien a l'état homogène. On peut employer des agitateurs mécaniques, électriques, semblables à celui dont nous avons publié la description, et qui se placent dans une grande chambre étuve.

Le procédé a été generalisé par P. Courmont et Descos a l'obtention des cultures homogènes de tous les bacilles acido-resistants[7]. Le milieu liquide le plus favorable est le bouillon glycériné a 5% (avec ou sans viande), peptoné a 2 % et salé a 1 %, et exactement neutralisé. Mais nous avons fait pousser nos cultures dans du bouillon ordinaire, comme Ferran, et même dans une simple solution de glycogène (P. Courmont). Jusqu'ici les bacilles homogènes se sont montrés uniquement aérobies.

La température optima est + 370 + 380 C. Mais P. Courmont a pu obtenir une végétation a + 20° et + 25° C[20], et S. Arloing a pu cultiver quelques uns de ces bacilles a + 44° en générations successives.

III. Morphologie-Coloration-Perte de l'acido-résistance.

Les bacilles sont isolés les uns des autres ou en très petits amas de quelques individus; en cultures jeunes ils sont nettement *mobiles*. La forme des bacilles varie un peu avec l'origine des cultures, mais surtout avec leur âge et les conditions de développement.

Une culture jeune non colorée montre de petits bacilles fins, de longueur variable, très réfringents, rectilignes; beaucoup présentent un petit branchement de façon a former un y inégal, et ceci est caractéristique pour un oeil exercé.

Dans les cultures agées, on voit en outre des bacilles renflés, bosselés, tres irréguliérs à formes actinomycosiques. Ces formes s'obtiennent bien plus rapidement et constamment dans les cultures a + 44° et sous pression (Arloing).

L'acido-résistance des bacilles est très modifiée dans les cultures jeunes; à ce moment un très grand nombre des bacilles, traités par les méthodes classiques, de Ziehl par example, se laissent décolorer par les acides. Par double coloration on voit alors des bacilles recolorés en bleu a côté de ceux qui ont conservé le rouge, et un observateur non prévenu croirait alors a une impureté de la culture. Mais si on laisse vieillir la même culture, on voit que presque tous les bacilles sont devenus acido-résistants et se comportent de la façon classique.

IV. Virulence.

Certains échantillons de bacilles homogènes gardent une virulence peu modifiée a l'égard du cobaye pendant au moins un certain nombre de générations. Mais, le plus souvent, les cultures homogènes ont une virulence très modifiée: elles sont peu ou pas virulentes pour le cobaye en injection sous-cutanée, mais elles sont très infectantes pour le lapin par injection intra-veineuse. Une dose relativement forte ($\frac{1}{2}$ cc pour 2 kilogr. de palin) tue l'animal en une ou deux semaines, parfois en quelques jours; les lésions se réduisent alors en apparence a de la congestion de la rate et du foie. Mais si on examine ces organes au microscope on met en évidence des lésions tuberculeuses; folliculaires seulement si l'animal est mort rapidement; avec cellules géantes si la survie est assez longue; si la dose a été assez petite pour laisser survivre encore plus longtemps l'animal, on trouve des lésions scléro-tuberculeuses des viscères. (Arloing)[16].

Chez le veau, on obtient également toute une série de lésions qui peuvent se réduire a des tubercules ou des follicules microscopiques sans lésions

apparentes á l'oeil nu[16]. Chez le chien, l'inoculation sous-cutanée de doses fortes et repétées produit des abcès froids sous-cutanés, souvent sans altération bien évidente da la santé de l'animal. Si on injecte 1 *cc* de culture homogène dans la plévre du chien, on produit une pleurésie soit séro-fibrineuse, soit hémorragique, soit purulente, soit parfois simplement fibreuse[17]; le liquide de ces pleurésies renferme des leucocytes et des cellules endothéliales bourrés de bacilles de Koch. Ces pleurésies guérissent le plus souvent très bien et sans laisser de traces. Chez tous ces animaux le pouvoir agglutinant est ordinairement très élevé.

V. Agglutinabilité et pouvoir Agglutinogène.

Nous avons distingué ces deux propriétés. *L'agglutinabilité,* ou propriété d'être agglutinée par un sérum convenable, est souvent très developpée dans ces cultures homogènes. C'est la base de la recherche du *pouvoir agglutinant* du sérum, du sèro-diagnostic et du séropronostic (Voir le rapport special de P. Courmont sur ce point a ce Congrès de Washington).[18] Mais il faut bien savoir que l'agglutinabilité est une propriété contingente du bacille de Koch comme de tous les microbes. Certaines cultures sont très agglutinables et également pendant des années: notre culture A est très agglutinable et sert depuis dix ans au séro-diagnostic non seulement à Lyon mais dans un très grand nombre de centres scientifiques en Europe.

D'autres cultures homogènes au contraire ne sont pas agglutinables par aucun sérum, même par le sérum des animaux à qui on les a inoculées Nous avions cherché il y a plusieurs années a établir des différences entre les tuberculoses bovine, humaine et aviaire par l'agglutination de nos différentes cultures homogènes (6 cultures en 1904).[19] Mais nous avons vu que si on trouve des différences, cela tient surtout a des différences d'agglutinabilité de certaines cultures vis a vis de n'importe quel sérum. Deux cultures aviaires et deux humaines se montrèrent également non-agglutinables, même par les sérums homologues (c'est a dire le sérum des animaux inoculés avec ces cultures); une culture humaine et une culture bovine se montrèrent également agglutinables soit par le sérum homologue, soit par le sérum des animaux inoculés avec les autres cultures. Les différences dans l'agglutination des cultures tiennent donc plus a leur agglutinabilité qu'a leur origine aviaire ou bovine, ou humaine. L'agglutinabilité d'une culture peut d'ailleurs exister d'abord et se perdre ensuite pour longtemps, peut-être pour toujours. Nous avons nettement constaté le fait pour notre culture humaine H qui, en[19] l'espace de deux ans, a perdu toute son agglutinabilité, et ne l'a pas retrouvée depuis quatre ans. Réciproquement, une culture peu ou pas agglutinable peut le devenir de plus en plus. Deux de nos cultures sont actuellement, en 1908, beaucoup plus agglutinables qu'en 1904.

Le pouvoir agglutinogène est la propriété, pour ces cultures, de déterminer

le pouvoir agglutinant du sang chez les animaux à qui elles ont été inoculées. Nous avons vu que toutes nos cultures sont agglutinogènes, lors même qu'elles ne sont pas agglutinables.

VI. En Résumé.

Les cultures homogènes du bacille de la tuberculose présentent un double intérêt, *pratique* et *théorique*. En pratique, elles permettent les applications de la séro-réaction. Au point de vue théorique, elles permettent d'étudier les transformations biologiques du bacille de Koch. Celui-ci, en cultures homogènes devient mobile, peu virulent, ou du moins de virulence modifiée, beaucoup moins acido-résistant, et enfin peut pousser dans des conditions de milieu et des températures bien différentes de celles qui lui sont habituelles. C'est au point que bien des différences s'effacent ainsi entre lui et d'autres microbes, par exemple les autres bacilles acido-résistants du beurre, du lait ou de la nature, et que l'on peut poser a ce sujet la question du saprophytisme du bacille de Koch[20].

1. S. Arloing, "Sur L'obtention de cultures et d'emulsions homogènes du bacille de la tuberculose humaine en milieux liquides," C. R. Académie des Sciences, Paris, 16 Mai, 1898.
2. Ferran, Société de Biologie, 1897.
3. S. Arloing et Paul Courmont, "De l'obtention des cultures du bacille de Koch les plus propres a l'étude du phenomène de l'agglutination," C. R. Académie des Sciences, 8 Aout, 1898.
4. S. Arloing et Paul Courmont, "Transformation du bacille de Koch d'origine humaine en une varieté possedant la plupart des caractères du bacille de la tuberculose aviaire," Congrès international de médecine, Paris, 1900.
5. Pour cette bibliographie voir le rapport de P. Courmont au Congrès de la tuberculose à Washington (section II): Pouvoir agglutinant chez les tuberculeux, Voir aussi spécialement pour les cultures homogènes: S. Arloing et P. Courmont. "Séro-diagnostic de la tuberculose," Zeitschrift für Tuberkulose u. Heilstätenwesen, Band I, Heft I, 1900.
6. Idem.
7. Paul Courmont et Descos, "Cultures liquides homogènes et mobilité des bacilles acido-résistants," Société de Biologie, 29 Novembre, 1902.
8. Paul Courmont, "Agitateur électrique pour l'obtention des cultures homogènes," Journal de physiol. et pathol. générales, Mai, 1903.
9. Paul Courmont et Potet, "Les bacilles acido-résistants du beurre, du lait et de la nature comparés au bacille de Koch," Archiv. de médecine experimentale, No. I, Janvier, 1903.
10. Auclair, Archiv. de médecine expérimentale, Juillet, 1903.
11. Ferran, Archives de médecine générale, Janvier, 1903.
12. Hawthorn, Société de Biologie, 1903.
13. Paul Courmont et Nicolas, Cultures liquides de tuberculose aviare, Société de Biologie, 1904.
14. S. Arloing et Paul Courmont, "Variations de l'agglutination des bacilles de la tuberculose, 2 memoires," Revue de la tuberculose, Juin et Octobre, 1904.

15. Rosenberger, "A Study of Homogenised Cultures of Tubercle Bacilli," American Medicine, April, 1905.
16. Voir: S Arloing: "Caractéristique anatomique de l'infection tuberculeuse," Académie des Sciences, Paris, 1908. Congrès de Washington, section 1, 1908.
17. Paul Courmont, "Pleurésies tuberculeuses expérimentales," Société des Sciences médicales, 28 Janvier, 1899. Voir: Lyon medical, 1899. Thèse de L'homme, Lyon, 1900.
18 Paul Courmont, "Le pouvoir agglutinant du sérum chez les tuberculeux. Séro-diagnostic, séro-pronostic," Congrès de la tuberculose de Washington, 1908, sect. II.
19. S. Arloing et Paul Courmont, "Variabilité de l'agglutination des bacilles de la tuberculose. 2 memoires," Revue de la tuberculose, Juin et Octobre, 1904.
20. Paul Courmont et Potet, "Les bacilles acido-résistants du beurre, du lait ét de la nature comparés au bacille de Koch," Archives de médecine expérimentale, Janvier, 1903.

Paul Courmont, "Saprophytisme du bacille de Koch," Congrès international de la tuberculose, Paris, 1905.

VARIATIONS DU BACILLE TUBERCULEUX.

(SPÉCIALEMENT AU POINT DE VUE DE LA VIRULENCE.)

PAR DR. S. ARLOING,

Lyon.

Avant d'aller plus loin dans l'examen de cette question, il n'est pas inutile de dire que la virulence du bacille tuberculeux se manifeste de plusieurs manières.

On admet généralement que la virulence se mesure à la facilité que possède le bacille à provoquer les édifications macroscopiques comme sous le nom de tubercules. Plus nombreux, plus étendus seront les tubercules consécutif à une inoculation, plus la virulence sera jugée grande; et inversement.

Nous avons fait remarquer antérieurement que les tubercules macroscopiques ne sont pas seuls à prouver la virulence spécifique d'un bacille; car cette virulence peut être modifiée de telle manière qu'elle ne permet plus au bacille de provoquer la formation de tubercules macroscopiques. Elle détermine, dans certains organes, des lésions d'un autre ordre, n'ayant qu'une partie des caractères du tubercule, et dont la recherche et l'étude exigent les procédés histologiques.

Parfois, même, ces lésions sont dépourvues de la caractéristique histologique du tubercule. Leur nature est révelée par des lésions situées dans d'autres organes du même sujet ou par la connaissance de la cause qui les a déterminées.

Enfin, les altérations causées par le bacille tuberculeux sont des processus histologiques si minimes que le microscope est, pour ainsi dire, incapable de les reconnaitre d'une façon certaine. On les soupconne plutôt qu'on ne les voit. L'Infection bacillaire est surtout indiquée par l'assistance de réactions expérimentales, telles que la sensibilité du sujet à la tuberculine et la présence de l'agglutinine spéciale dans le sérum sanguin.

La virulence se manifeste encore par le pouvoir tonique des émulsions de bacilles dans l'eau salée ou des cultures complètes en bouillon glycériné. J'ai insisté, il y quelques années sur les accidents immédiats causés par l'injection de ces émulsions dans les veines, et montré que la toxicité a des rapports étroits avec la virulence des bacilles.

Donc, le bacille tuberculeux, ayant des caractères pathogéniques multiples, il conviendra de chercher les variations de sa virulence en s'inspirant de la multiplicité de ces caractères. Certains points de cette étude complète sont encore à peine ébauchés. Néanmoins, les notions acquises actuellement suffisent à étayer solidement le principe même de ces variations, de sorte que l'on l'en pourrait presque s'étonner de le voir réunis en question.

Je commencerai par déclarer que, dans ma conviction intime le bacille de la tuberculose est un, et que des espèces ou des types reconnus et défendus par quelques observateurs ne sont que les races ou des variétés temporaires, dont l'apparente fixité ne dure guère plus que les conditions de milieux ayant présidé à leur formation.

Par exemple, je ne crois pas qu'il existe un type humain et un type bovine rigoureusement défini et séparable parmi les bacilles des mammifères.

De même, je ne crois pas qu'il soit impossible d'apparenter entre eux le type aviaire et le type pisciaire et de les types rapprocher des bacilles des mammifères. J'admete, au contraire, grâce à l'étude attentive, et sans parti pris, des variations qui nous sont offertes par la nature qui résultent d'agents modificateurs artificiels que ces types tendent à se rapprocher et à se confondre en un type commun. La malléabilité des types est telle, à ce jour, qu'il est légitime de prejuger qu'elle grandira avec le perfectionnement de nos moyens d'étude et que bientôt fléchira la résistance des observateurs qui plaident encore pour la fixicité des types.

Mais le point de vue philosophique n'est peut être pas le plus intéressant par un congrès international de la tuberculose. Aussi n'insisterai-je pas sur ce point de vue. Je glisserai même sur des variations du bacille des animaux à sang froid. A ce propos je renverrai le lecteur à mes publications antérieures. (1). J'examinerai plus particulièrement le bacille de la tuberculose des mammifères et celui de la tuberculose des oiseaux.

Variations du Bacille dans La Tuberculose Humaine.

Sur la variabilité repose le principe qui sert de base aujourd'hui à tous les essais d'immunisation active contre la tuberculose.

Voici dans quelles conditions j'ai fait mes premières observations.

J'avais inoculé des lapins et des cobayes sous la peau avec du virus emprunté à des ganglions strumeux et à des lésions pulmonaires. Je constatai ensuite que les lapins et les cobayes infectés avec du virus pris dans les poumons, devenaient tuberculeux tandis que parmi les animaux inoculés avec le virus strumeux, les cobayes seulement présentaient une tuberculose locale et générale.

M'appuyant sur l'inégalité de résistance du lapin et du cobaye à la tuberculose, j'ai conclu que les ganglions scrofuleux relevaient d'un variété de tuberculose moin virulente que la tuberculose pulmonaire.

Ma conclusion a été vivement attaquée. On s'en apercevra en parcourant les comptes-rendus des divers congrès français de la tuberculose et le bel ouvrage de Straus, "La tuberculose et son bacille."

On voulait attribuer la différence que j'avais observée non à une variation dans la virulence des bacilles, mais à une variation de leur nombre dans les lésions inoculées.

Bientôt, ayant étendu mes expériences à un grand nombre de formes de tuberculose chirurgicale, je ne tardai pas à m'apercevoir qu'il y en est, parmi ces tuberculoses chirurgicales, même ganglionnaires, d'aussi virulentes que les lésions pulmonaire typique, d'autres aussi atténuées que la scrofule, et quelques-unes dont la virulence était intermédiaire entre ces deux extrêmes, virulence qu'il était possible de relever par deux ou trois passages sur le cobaye.

Aussi ai-je admis qu'il existe des tuberculoses chirurgicales capables de tuberculiser d'emblée le lapin et le cobaye, d'autres qui tuberculisent le lapin après plusieurs passages sur le cobaye, et certaines dont le pouvoir tuberculique est incapable de s'exercer sur le lapin. Dans leur ensemble, elles présentent une gamme de virulence typique jusqu'à celle qui exige le cobaye pour se manifester plus ou moins nettement. Le nombre des variétés est donc théoriquement indéterminé.

La variabilité ne se limite pas au virus des tuberculoses chirurgicales ordinaires, j'en ai montré également la présence avec Jules Courmont, dans les lupus tuberculeux. On affirmait que les granulations lupiques voulaient être insérées dans le peritoine en la chambre antérieure de l'oeil pour donner une inoculation positive. Or, nous avons rencontré des granulations lupiques capables de tuberculiser le lapin et le cobaye par inoculation sous-cutanée après passage dans le peritoine du cobaye. Et l'un de nos élèves, le Prof. Nicolas, de Lyon, a trouvé un lupus inoculable d'emblée sous la peau.

Le virus pulmonaire lui-même n'échappe pas à la variabilité. Des recherches faites autrefois dans mon laboratoire par Jules Courmont et Denis, établient que le virus de certaines tuberculoses pulmonaires n'est pas plus actif que celui de la majorité des tuberculoses chirurgicales.

En résumé, dans les trois grandes divisions de la tuberculose humaine, tuberculose pulmonaire, tuberculose, cutanée, tuberculose chirurgicale, c'est à dire ganglionnaire et ostéo—articulaire, la virulence est sujette à de grandes variations. Ajoutons que les tuberculoses chirurgicales se rattachent en plus grand nombre aux variétés les moins virulentes et les tuberculoses médicales aux variétés les plus virulentes.

On se rappelle qu' au Congrès de la tuberculose de Londre, en 1901, Koch et Schütz tentèrent de faire accepter une différence radicale entre le bacille d'origine humaine et le bacille d'origine bovine.

J'avais de bonnes raisons pour ne pas admettre les idées de ces savants.

Néanmoins, j'ai entrepris des expériences de vérification. (1) Elles ont consisté à étudier les effets de plusieurs bacilles humains, en cultures pures, tirés des lésions thoraciques de malades différents. J'insiste sur la permanence de ces bacilles, afin d'écarter les doutes que pourrait avoir les bactériologistes de l'école de Robert Koch sur la nature de ces microbes, s'ils avaient été empruntés à des lésions de l'appareil digestif. Je veux dire qu'ils ne proviennent pas d'un foyer que les auteurs précités attribueraient à une contamination directe par des bacilles d'origine bovine.

La comparaison entre ces divers bacilles était rendu possible grâce aux conditions observées dans l'expérimentation: les doses étaient identiques pour chaque bacille et pour les animaux de la même espèce; les injections étaient poussées dans la voie sanguine, la plus sure, la moins sensible à l'influence du sujet; elles ont été faites, pour chaque bacille, sur des boeufs, des moutons et des chèvres de même age et, en outre, l'inoculation était répétée sur des lapins et des cobayes, par des voies diverses, à titre de renseignement. D'après l'étendre à la forme des lésions obtenues, je me suis assuré que les bacilles inoculés possédaient une virulence très différente, bien qu'ils soient tous d'origine humaine. Deux se sont montrés aussi virulents que des bacilles bovins très actifs; les autres étaient moin nocifs; au lieu de produire une tuberculose pulmonaire confluente rapidement mortelle, ils se bornaient à produire des granulations tuberculeux discrètes dans le poumon coexistant avec un état général assez satisfaisant. Il en était enfin dont l'inoculation semblait avoir été négative; mais l'examen histologique du foie, de la rate, des reins et même du poumon, révelait des lésions microscopiques, démontrant une infection tuberculeuse généralisée. Ce sont ces lésions qui m'ont fait dire, depuis plusieures années, combien il était utile de chercher les altérations par la technique histologique avant de se prononcer sur les suites d'une inoculation, lorsque le poumon ne contenait pas de lésions macroscopiques. Les variations de la virulence du bacille humain, sans des influences modificatrieux spontanées, se trouvent donc parfaitement etablies. Celles qu'il m'a été donné d'observer dans les expériences rappelées ci-dessus, sont elles les seules que l'on puisse rencontrer?

Assurément non. Il doit exister des bacilles que leur virulence placerait entre les nôtres ou à leur suite. Bien plus, les influences que les bacilles humains peuvent subir dans le monde extérieur ou dans les organismes vivants, sont non seulement capables de modifier la virulence classique, mais encore d'imprimer à celle-ci des modalités particulières.

Il en résultera des termes nouveaux dans la langue de la virulence des bacilles, dont j'admet théoriquement l'existence, puisque je les ai obtenus par des moyens artificiels. J'ai annoncé au Congrès de Médicine de Montpellier, en 1898, que j'avais accoutumé le bacille humain à se multiplier dans la profondeur du bacille glycériné, de manière à obtenir des cultures homo-

gènes, c'est à dire distribuées uniformément dans toutes leurs parties. (Quelques mois auparavant Ferran, de Barcelone, avait obtenu des cultures analogue, à mon insu.) C'est à l'aide de ces cultures que j'ai montré le pouvoir agglutinant du sérum des tuberculeux sur le bacille de Koch, pouvoir que j'ai étudié ensuite d'une manière très approfondie avec mon élève, Paul Courmont. Mais il ne sera pas question ici de l'agglutinabilité des bacilles ni des variations de leurs caractères morphologique. Je fixerai simplement l'attention sur la modalité particulière sous laquelle se présente la virulence du bacille des cultures homogènes faites à 37°.

Avant d'être soumis à son nouveau mode de végétation, le bacille tuberculisait les cobayes et les lapins comme la moyenne des bacilles d'origine humaine. Après, il était incapable de tuberculiser ces animaux par inoculation sous-cutanée. Injecté dans les veines du lapin, il tient cet animal à la façon du bacille aviaire, en lui infligeant une cachexie intense, l'hypertrophie de la rate et des lésions hépatiques du type Yersin. L'aspect extérieur du foie reste normal.

En 1900, J'avais appelé cette infection "tuberculose septicémique." C'était à tort; car à dose moyenne ou faible, la culture homogène, inoculé dans une veine, produit toujours quelques lésions plus ou moins perceptibles au microscope. Dans le foie, elles consistent en une infiltration de petites cellules rondes dans la partie périphérique ou centrale des lobules, renaissant, refoulant les éléments nobles de l'organe. Le plus souvent l'infiltration n'est pas accompagnée de cellules géantes. Dans la rate, on voit des cellules epithélioïdes à l'intérieur en dehors des follicules, disséminées ou groupées en amas figurant vaguement des tubercules, accompagnées ou non de cellules géantes. Dans les reins, on relève des lésions de néphrite interstitielle envahissant par place la couche corticale. Le poumon ne fait pas exception; il peut renfermer quelques infiltrations vaguement nodulaire. À dose très faible, les altérations microscopique du foie, de la rate et du poumon peuvent échapper entièrement ou presque entièrement au microscope.

La modalité produite dans la virulence du bacille par son accoutumance à vivre en culture homogène a surpris certains expérimentateurs à ce point qu'ils ont mis en doute l'origine de ce bacille.

Je puis les rassurer. Effectivement, au moment propice, on découvre des bacilles à réaction colorante spécifique dans des lésions, de plus, inoculé dans le peritoine, il engendre des tubercules véritables dans l'epiploon et dans des ganglions satellites des artères gastro-epiploïques.

Cette variété qui se propage admirablement dans du bouillon glycériné à la température de 37° est relativement plus active sur le boeuf que sur la chèvre. Partant de cette variété expérimentale, j'en ai créé une seconde en habituant très progressivement les cultures à végéter à 44°, puis à 45½°.

Propagé à cette température, le bacille est moins dangereux pour le lapin. L'animal survit plus longtemps; il présente des lésions hépatiques beaucoup plus discrètes; néanmoins, il a bien été en conflit avec un bacille tuberculeux, car au but de dix mois, à un an de survie, il est frappé souvent de synovite spéciale articulaire ou tendineuse ayant tous les caractères histologiques désirables.

En m'efforçant dans la même voie, j'ai relevé, au contraire, la virulence des cultures homogènes primitive. Il m'a suffi pour cela de soumettre plusieurs générations successives à la pression de 2 Kos $\frac{1}{2}$ et de 3 Kos $\frac{1}{2}$.

Sous cette pression et à la température de 37°, les cultures sont très abondantes, les bacilles qui les garnissent ont perdu une grande partie de leur acido-résistance, mais en revanche ils ont acquise une virulence plus grande. Celle-ci se manifeste sur le lapin, à la suite des injections dans la veine. Le sujet meurt plus vite et présente des lésions hépatiques et spleniques beaucoup plus étendues où l'on voit de nombreuses cellules géantes; en outre, le poumon est envahi par de multiples foyers microscopiques où les cellules géantes se dessinent avec netteté.

Il n'est donc pas douteux qu'une atmosphère d'air comprimé, favorable à la pullulation des bacilles défavorables à la formation de leur substance acido-résistante, relève la virulence des bacilles en culture homogène sans leur restituer toutefois la modalité dans la virulence qu'ils possédaient dans leurs anciennes cultures sur pomme de terre glycériné.

La virulence, soit dit en passant, n'a pas de rapport étroit avec l'acido-résistance. Je l'avais déjà signalé dans mon rapport du Congrès de Berlin.

D'autres preuves de la malléabilité du bacille humain seraient fournies par les travaux de Terre, de Lubarsch, de Moeller, sur les effets du passage du bacille dans l'organisme de la carpe, de la grenouille et de l'orvet, s'il était nécessaire de les accumuler en plus grand nombre.

Variations du Bacille dans la Tuberculose Bovine.

Des remarques présentées avec mesure par Theobald Smith, puis par Gaiser, Dinwiddie, Frothingham, ont suggéré à R. Koch et Schütz d'établir une séparation tranchée entre le bacille humain et le bacille bovin. On connait la solution du débat soulevé par ces savants; je n'y insisterai pas.

Je me bornerai à retenir que R. Koch et Schütz attribuaient au bacille bovin une virulence fixe d'où ils tiraient un critérium pour nous le faire reconnaitre, surtout dans les cas où il se serait accidentellement implanté dans l'organisme de l'homme.

D'après ces deux auteurs, le bacille tuberculeux est d'origine bovine lorsqu'il est capable de produire une tuberculose généralisée sur le veau, à la suite de l'inoculation sous-cutanée. D'après les mêmes auteurs le bacille d'origine humaine ne produirait pas de tuberculose généralisée sur le veau,

quel que soit le mode d'inoculation. Ce critérium exposerait à beaucoup d'erreurs si on l'estimait impeccable.

Certaines souches de bacilles bovins possèdent bien la virulence signalée par Koch et Schütz, mais j'en ai rencontré un bon nombre dont l'inoculation sous-cutanée produisait un accident plus ou moins accusé au point d'insertion et la tuberculisation des ganglions lymphatiques venant de la région inoculée. J'ai conservé des veaux pendant six, huit et dix mois après l'inoculation; le processus est resté localisée comme il est dit précédemment.

La dernière Commission royale anglaise pour l'étude du problème de l'unité ou de la dualité de la tuberculose humaine et bovine a fait des constatations analogues. De plus, elle a isolé certaines souches de bacilles bovins dont les lésions étaient intermédiaires entre les lésions généralisées et les lésions localisées.

Donc la virulence du bacille bovin peut varier sous l'influence de causes naturelles. Varierait-elle aussi sous l'influence de causes artificielles? Oui. Si je ne voulais abréger ce mémoire, j'aurais à répéter ici tout ce que j'ai déjà dit de l'influence de la végétation dans la profondeur du bouillon glycériné sur la virulence du bacille humain. J'ai conduit mes expériences parallèlement sur des bacilles humains et des bacilles bovins. J'ai obtenu dans les deux séries des modifications analogues.

Je ferai simplement remarquer:

1. Que le bacille du boeuf se modifie un peu plus difficilement que le bacille de l'homme.

2. Que le bacille bovin modifié est plus nocif sur le veau et le mouton que le bacille humain.

Je conclurai donc en affirmant que la virulence des bacilles du boeuf présente des variations indiscutables qui s'établissent sous des influences modificatrices naturelles et expérimentales.

Variations des Bacilles de la Tuberculose Aviaire.

La virulence du bacille des oiseaux n'échappe pas non plus à la variation. On ne peut pas s'incliner aujourd'hui devant l'ancienne caractéristique, d'après laquelle un bacille aviaire doit infecter les gallinacés par toutes les voies d'inoculation et échouer en présence de l'organisme des mammifères à moins qu'il ne soit introduit dans les veines du lapin, auquel cas il détermine une tuberculose du type Yersin.

En effet, on peut retirer des oiseaux, des bacilles qui ne manifestent pas une égale virulence sur les gallinacés. Par exemple, j'entretiens quatre souches qui toutes provoquent la tuberculisation de la rate et du foie après inoculation dans les veines de la poule, mais ne se comportent pas de la même façon lorsqu'on les inocule par d'autres voies. Trois n'ont rien produit dans le peritoine, la quatrième a déterminé les fausses-membranes où l'on n'aper-

cevait pas de tubercules. Trois ont paru échouer sous la peau; la dernière provoqua localement un abscès casséeuse dans lequel fourmillaient des bacilles granuleux.

Les variations de la virulence sont encore démontrées lorsqu'on inocule les bacilles aviaires aux mammifères. Von Behring a possédé des bacilles aviaires tuberculisant d'emblée le cobaye, le lapin et le boeuf, animaux dont la résistance à la tuberculisation est très inégale. Lydia Rabinowitsch, qui a poursuivi des nombreuses recherches sur ce point, a rencontré des bacilles aviaires dont la virulence était semblable à celle du bacille humain.

A. de Jong a infecté le boeuf, la chèvre et le porc à des degrés divers en leur faisant ingérer des bacilles aviaires.

Beaucoup d'expérimentateurs français, notamment Grancher et Ledonn-Lebard, J. Courmont et Dor, Cadiot, Gilbert et Roger, Gratia, ont observé sur des lapins inoculés avec des bacilles aviaires et qui avaient échappé à l'infection aiguë du type Yersin, des lésions tuberculeuses du type Villemin.

J'ai essayé moi-même cinq bacilles aviaires sur le cobaye et le lapin: tous ont produit sur ce dernier animal des lésions hépatiques par injection intraveineuse; deux sur cinq ont tuberculisé l'epiploon et les ganglions périgastriques par inoculation intra péritonéal; un a produit la tuberculisation des ganglions pré-cruraux et sous lombaires du cobaye à la suite d'une inoculation faite sous la peau de la cuisse; enfin un autre a tuberculisé complètement le cobaye après une inoculation semblable.

Ajouterai-je que l'on a trouvé dans des lésions tuberculeuses de l'homme, du cheval, de la souris, du porc, du singe, du lapin des bacilles ayant les caractères habituels du bacille aviaire. Ces faits dûs à des observateurs différents prouveraient que la virulence du bacille aviaire est quelquefois assez grande pour infecter des mammifères. Les variations mentionnées ci-dessus sont toutes spontanées. Il me reste à dire que l'on en peut réaliser expérimentalement. Si, à l'exemple de J. Courmont et Dor, de Gilbert et Roger, on fait passer plusieurs fois un bacille aviaire sur un mammifère, on exalte la virulence pour ce mammifère, tandis qu'on la voit diminuer pour les oiseaux. Si, au contraire, on propage ce bacille exalté sur l'organisme de la poule, la virulence diminue pour les mammifères.

Il n'est pas nécessaire d'allonger cet exposé de faits. Tel quel, il suffit à démontrer que le type aviaire classique peut se trouver dans la nature avec une virulence variée, virulence qui, parfois, ne le cède en rien à celle du bacille humain et même à celle du bacille bovin.

Conséquences Pratiques.

Les variations de la virulence du bacille tuberculeux, que je juge parfaitement établies, sont intérressantes pour la médecine et pour l'hygiène. Au point de vue médicale, elles nous expliquent les différences considérables qu'offre du tuberculose sous le rapport de sa gravité et de son évolution.

Si des différences peuvent tenir au terrain, c'est à dire à la résistance ou à la défense de l'organisme infecté, elles dépendent aussi, pour une part indéniable, de la virulence du bacille et de la modalité de cette virulence.

Les formes les moins graves de la tuberculose s'observent parmi les tuberculoses chirurgicales. L'étude des variations en a donné la raison. Mais elle a donné en même temps la raison des exceptions relevées par les chirurgiens, puisque j'ai montré que dans quelques tuberculoses chirurgicales existe un virus très-actif. Elle permet aussi de se rendre compte des évolutions très-variées des tuberculoses pulmonaires.

De sorte qu'après les progrès réalisés pour poser expérimentalement le diagnostic de la tuberculose, on éprouve le besoin de posséder des moyens de diagnostic.

Les moyens révèlateurs ne fournissent aucun renseignement sur le mode d'infection, le siège des lésions et la virulence du bacille engagé dans l'infection. Cependant, l'avenir d'une infection tuberculeuse dépend en grand partie de la virulence de l'agent infectieux, il importerait d'être renseigné sur cette virulence. Comme il dépend aussi de la réaction de l'organisme à l'infection, il serait également utile d'apprécier la valeur de cette réaction. J'ai fait connaitre un procédé pour distinguer un virus tuberculeux fort d'un virus tuberculeux relativement atténué; il consiste à inoculer simultanément et comparativement dans le tissu conjonctif du lapin et du cobaye. Il répand à l'un des desiderata exprimés cidessus.

La séro-agglutination tuberculeuse que j'ai introduite dans la science et perfectionnée avec Paul Courmont permet d'apprécier, mieux que tous les autres procédés de diagnostic, la réaction ou la défense de l'organisme, aussi que Fernand Arloing le montrait tout récemment. Enfin, la même étude établit scientifiquement la possibilité d'une infection tuberculeuse sans lésions evidente macroscopique ou microscopique, capable de guérir sans laisser la moindre séquelle. Cette forme de l'infection ne pourra pas être reconnue sans le secours des procédés de diagnostic expérimentaux. Ceux-ci dénoncent donc l'infection tuberculeux plutot que les tubercules.

Telles sont à première vue des variations de la virulence du bacille tuberculeux.

Au point de vue de l'hygiène, elles nous amènent à l'unicité de la tuberculose, à la fusion des types classiques, et à l'utilité de prendre des mesures contre le virus tuberculeux partout où il est et d'où qu'il vienne.

INDICATIONS DES TRAVAUX DE S. ARLOING CITÉS OU UTILISÉS DANS LE PRÉSENT MÉMOIRE.

1. Expériences comparatives sur l'inoculabilité de la scrofule et de la tuberculose au lapin et au cobaye. C. R. de l'Acad. des Sci., 1887.
2. Influence de l'organisme du cobaye sur la virulence de la tuberculose et de la scrofule. C. R. de l'Acad. des Sci., 1886.

3. Essai sur la différentiation expérimentale de la scrofule et de la tuberculose humaines. Revue de Médecine, 1887.
4. De l'inoculation aux animaux comme élément du diagnostic et du pronostic de la tuberculose de l'homme. Congrès pour l'étude de la Tuberculose, Paris, 1888.
5. Leçons sur la Tuberculose. 1 vol., Paris, 1892.
6. Sur les dégrés de la virulence du lupus (en collaboration avec J. Courmont). Congrès français de la Tuberculose, Paris, 1893.
7. Tuberculose pulmonaire à bacilles atténués; méthode de pronostic expérimental. Thèse de Denis, Lyon, 1894.
8. Agglutination du bacille de la tuberculose vraie. Congrès français de Médecine interne, Montpellier, 1898.
9. Sur l'obtention de cultures et d'émulsions homogènes du bacille de la tuberculose humaine en milieu liquide et sur une variété mobile de ce bacille. C. R. de l'Acad. des Sci., 1898.
10. Démonstration expérimentale de la prédisposition créé par la tuberculose septicémique ou infectieuse vis à vis d'elle-même. Congrès international de Méd., Paris, 1900.
11. Transformation du bacille de Koch d'origine humaine en un variété possédant la plupart des attributs du bacille de la tuberculose aviaire. Congrès international de Méd., Paris, 1900.
12. Examen critique des idées de M. R. Koch sur la lutte contre la tuberculose humaine. Revue de la Tuberculose, 1900.
13. L'inoculabilité de la tuberculose humaine et les idées de M. Robert Koch sur cette tuberculose et la tuberculose animale. Bulletin de l'Acad. de Méd. de Paris, 1900.
14. Unité de la tuberculose humaine et de la tuberculose bovine. Presse Médicale, 1902.
15. Démonstration de l'unité de la tuberculose humaine et de la tuberculose bovine. Conférence internat. de Berlin pour la lutte contre la Tuberculose, 1902.
16. La tuberculose humaine et celle des animaux domestiques sont elles dues à la même espèce microbienne; le bacille de Koch? Rapport au Congrès internat. d'hyg. et de démograph., Brussels, 1903.
17. Du diagnostic histologique de la tuberculose expérimentale chez les mammifères domestiques. (En collab. avec Paviot.) Revue de la Tuberculose, 1904.
18. Étude comparative des diverses tuberculoses. Rapport au Congrès internat. de la Tuberculose, Paris, 1905.
19. Sur l'indication des voies digestives pour la vaccination antituberculeuse des jeunes ruminants. (en collab. avec Stazzi.) C. R. de l'Acad. des Sci., 1906.
20. Production expérimentale de variétés transmissibles de bacilles de la tuberculose et de vaccins antituberculeux. C. R. de l'Acad. des Sci., 1906.
21. Variabilité du bacille de la tuberculose. Rapport au Congrès internat, d'hyg. et de démograph., Berlin, 1907.
22. Variabilité du bacille de la tuberculose. Revue de la Tuberculose, 1908.
23. Des caractères de l'infection tuberculeuse dans leurs rapports avec le diagnostic de la tuberculose par des moyens révélateurs. C. R. de l'Acad. des Sci., 1908.

LA VIRULENCE DES BACILLES DANS SES RAPPORTS AVEC LA MARCHE DE LA TUBERCULOSE PULMONAIRE.

Par Dr. A. Rodet et P. Delanoë,
Montpellier.

Les mémorables recherches d'Arloing sur les tuberculoses dites chirurgicales ayant attiré l'attention sur l'inégalité de virulence des bacilles dans la tuberculose humaine, un travail de Denis ouvrit la voie aux recherches sur les bacilles de la tuberculose pulmonaire au point du vue de leur degré de virulence. Depuis lors, la question a fait l'objet, surtout à l'étranger, d'un certain nombre de travaux, dont les conclusions ne sont pas très concordantes. Nous nous sommes proposé de nouvelles recherches sur ce point, en prenant comme objectif principal les relations entre la virulence des bacilles et l'évolution clinique ou la marche des cas d'où ils proviennent. En d'autres termes, nons avons cherché dans la mesure de la virulence des bacilles fournis par un nombre aussi grand que possible de tuberculeux pulmonaires, une réponse à cette question; la marche si variable de la tuberculose pulmonaire s'explique-t-elle uniquement ou surtout comme le pensent nombres de cliniciens, par l'inégalité de résistance des sujets, ou, suivant l'expression accoutumée par l'influence du terrain? Ne faut-il pas penser que, conformément à une loi absolument générale en pathologie infectieuse expérimentale, un rôle important, sinon prépondérant, revient à l'inégale virulence des bacilles?

Nos recherches ont porté sur 28 malades, atteints des formes les plus diverses de tuberculose pulmonaire, depuis les cas les plus aigus jusqu'aux formes les plus prolongées, tous porteurs de bacilles dans les crachats. Les observations ont été prises avec détails; ceux des malades qui ne sont pas morts ont été suivis le plus longtemps possible, revus en dehors de l'hôpital à plusieurs reprises.

La virulence des bacilles a été déterminée par la série d'operations suivantes: inoculation des crachats à des cobayes; avec les ganglions de ces cobayes, sacrifiés aprés trois semaines environ, culture sur sérum de mouton glycériné; après un séjours suffisant à l'étuve, reproductions de ces cultures sur pomme de terre glycérinée; épreuve de la virulence de ces dernières cultures, toujours au même âge (1 mois). Comme réactif du virulence,

nous avons employé dans tous les cas simultanément le lapin et le cobaye; le choix du lapin s'impose, depuis que les recherches d'Arloing ont montré qu'il révèle des inégalités de virulence que le cobaye ne décèle pas suffisamment. Les cultures ont été injectées sous la peau de la cuisse, en quantité toujours la même (au cobaye $\frac{1}{4}$ cm. (3), au lapin $\frac{1}{2}$ cm. (3) d'une émulsion à raison de 0.20 gr. des bacilles humides pour 10 cm. (3). Exceptionnellement, par surcroît, nous avons eu recours à l'injection intraveineuse au lapin. Les cobayes étaient généralement laissés à l'évolution naturelle, conservés jusqu'à leur mort; les lapins, sacrifiés après deux mois environ.

Nous avons pu ainsi étudier complètement les bacilles de 26 malades sur 28. Dans 2 cas, les crachats, quoique ayant donné un résultat positif à l'examen microscopique, n'ont pas tuberculisé le cobaye et n'ont déterminé chez lui que des lésions insignifiantes qui n'ont pas permis d'isoler le bacille.*

Le premier fait saillant qui ressort de notre étude, c'est que les bacilles se sont montrés très inégaux en virulence.

Sur le lapin, les différences ont été très tranchées: sur nos 26 bacilles isolés:

5 ont déterminé chez les deux lapins d'épreuve des lésions locales et pulmonaires graves;

6 ont déterminé chez les deux lapins d'épreuve une grosse lésion locale, et chez 1 lapin sur 2 une grave lésion pulmonaire (l'autre lapin présentant des poumons soit indemnes, soit atteints de lésions discrètes);

6 ont déterminé chez les deux lapins d'épreuve une lésion locale et des lésions pulmonaires discrètes;

5 n'ont déterminé dans le même temps (2 mois) chez les deux lapins que des lésions locales;

4 n'ont même pas provoqué de lésions locales.

Sur le cobaye, les 26 bacilles se sont montrés tous capables de déterminer une infection générale, mais avec de gros écarts dans la rapidité d'évolution. C'est ainsi que, pour ne parler que des extrêmes, certains bacilles ont provoqué la mort en 1 mois avec des lésions généralisées, d'autres ont laissé survivre les sujets 6 mois et plus; certains sujets, sacrifiés après 4 mois, avaient des poumons à peine touchés; d'autres, sacrifiés au bout de 3 mois, n'avaient encore que des lésions locales.

Comme on le sait, la durée d'évolution n'est jamais rigoureusement semblable dans un lot de cobayes infectés par le même bacille. Mais cet écart, qui témoigne de certaines inégalités dans la résistance individuelle des sujets, a rarement été considérable dans nos expériences; et il parait permis

* Nous ne tenons pas compte de quelques malades donts les crachats ont tuberculisé le cobaye, mais dont nous n'avons pas réussi à obtenir les bacilles en culture pure, les ensemencements faits avec les lésions des cobayes étant restés stériles.

de définir le degré de virulence de chacun de nos bacilles pour le cobaye par un chiffre en rapport avec la moyenne de survie des 3 cobayes d'épreuve. Nous pouvons de la sorte, en égard à la virulence pour cette espèce, établir dans nos bacilles une échelle, dont le premier degré répond aux bacilles qui nous ont donné une survie moyenne de moins de 2½ mois, et le cinquième degré à ceux qui ont procuré une survie moyenne supérieure à 4 mois. Cela nous permet de mettre en parallèle la virulence appreciée par le cobaye et la virulence appreciée par le lapin.

En rapprochant les deux échelles de virulence, graduées de 1 à 5 dans le sens de l'activité décroissante, nous constatons que le parallèlisme entre la virulence pour le cobaye et la virulence pour le lapin n'est pas absolu, mais n'est cependant pas complètement en défaut. Les deux échelles concordent à peu près complètement dans leurs degrés extrèmes (voir le tableau): les cinq bacilles occupant le premier degré dans l'échelle de virulence pour le lapin occupent aussi, sauf un, le premier degrè dans l'échelle de virulence pour le cobaye; les bacilles denués d'action pathogène pour le lapin, tout en étant capable de tuberculiser le cobaye, sont au dernier rang dans l'échelle relative à cette espèce. La concordance est inconstante dans les degrés intermédiaires: les bacilles de virulence moyenne pour le lapin occupent dans l'échelle de virulence pour le cobaye des places très différentes.

Quant aux 2 cas dont les crachats n'ont pas tuberculisé le cobaye, faut-il considérer les bacilles que contenaient ces crachats comme des bacilles plus attenués encore que les moins virulents des précédents? La question se pose; mais il est permis d'hésiter à faire de ces bacilles de vrais bacilles tuberculeux.*

Remarquons incidemment que nos bacilles se sont aussi distingués les uns des autres par d'autres caractères: aspect plus ou moins sec ou plus ou moins gras des cultures, rapidité de végétation, couleur, etc.; quelques-uns nous ont donné du moins sur certaines pommes de terre, des cultures fortement pigmentées (jaune d'or) aussi colorées que des cultures de bacilles de la phléole. Une particularité curieuse, c'est que certains échantillons, aprés avoir fort bien végété pendant quelques générations de cultures, se sont refusés à pousser sur pomme de terre glycérinée; ils purent cependant tuberculiser le cobaye, et le passage en cobaye leur rendit leur végétabilité.

Y-a-t-il une relation entre la virulence des bacilles et la marche des cas d'où ils proviennent? Pour répondre à cette question, nous condensons nos observations dans le tableau suivant.

On voit que, dans le premier groupe, aux bacilles très virulent pour le lapin (presque tous, sauf un, d'activité également maxima pour le cobaye)

* Les minimes lésions (exclusivement pulmonaires) que dans ces deux cas les crachats ont déterminé chez le cobaye étaient identiques à celles que donnent les inoculations en série de bacille de la phléole.

TABLEAU.

Nos. des Cas.	Durée de la Maladie.			Observations.	Virulence des bacilles Moyenne de Virulence.		
	Moins de 1 an.	De 1 à 4 ans.	Plus de 4 ans.		D'après le lapin.	D'après le cobaye.*	Pour les deux espèces.
1	Moins de 7 mois.	....	....	Pas d'hérédité tuberculeuse; alcoolisme.	1	1	1
2	5 mois.	....	....	Hérédité tuberculeuse; alcoolisme.	1	1	1
3	5 mois.	....	....	Hérédité alcoolique.	1	1	1
4	4.5 mois.	....	....	Pas d'hérédité; affection médullaire.	1	3	2
5	....	....	Plus de 22 ans.	Forme bronchitique.	1	1	1
6	4 mois.	....	....	Tabétique; cachectique.	2	3	2.5
7	....	20 mois.	....	Pas d'hérédité; altération rapide de l'état général.	2	2	2
8	....	4 ans.	....	Lésions graves bien supportées.	2	2	2
9	....	....	Plus de 4 ans.		2	2	2
10	5 mois.	....	....	Pas d'hérédité; alcoolisme; altération rapide de l'état général.	2	2	2
11	....	....	Plus de 12 ans.		2	2	2
12	....	....	Plus de 20 ans.	Hérédité; forme bronchitique.	3	1	2
13	....	....	Plus de 8 ans.	Série de poussées aiguës.	3	3	3
14	....	....	Plus de 4 ans.	Pas d'hérédité; grossesses.	3	4	3.5
15	....	....	Plus de 42 ans.	Pas d'hérédité; alcoolisme; lésions minimes mal tolérées.	3	4	3.5
16	....	1 an.	....	Pas d'hérédité; ni d'alcoolisme.	3	1	2
17	....	Moins de 2 ans.	....	Tempérament lymphatique.	3	1	2
18	....	1½ an.	....	Pas d'hérédité; altération rapide de l'état général.	4	2	3
19	....	....	Plus de 5 ans.	Pas d'hérédité; lésions bien tolérées.	4	?	?
20	....	1½ an.	....		4	3	3.5
21	....	Plus de 2 ans.	....	Alcoolisme; forme bronchitique.	4	2	3
22	....	....	Plus de 4 ans.	Episode aigu terminal.	4	5	4.5
23	....	....	Plus de 7 ans.	Pas d'hérédité; misère.	5	5	5
24	....	....	Plus de 6 ans.	Pas d'hérédité; alcoolisme.	5	5	5
25	....	....	Plus de 4 ans.	Pas d'hérédité; pas d'alcoolisme.	5	5	5
26	....	....	Plus de 14 ans.		5	5	5

* 1: survie moyenne des cobayes 2 mois à 2½ mois; 2: survie 2½ à 3 mois; 3: survie 3 mois à 3½ mois; 4: survie 3½ mois à 4 mois; 5: survie plus de 4 mois.

correspondent presque uniquement des formes très aiguës. Il y a une exception, un cas chronique; mais c'est une forme bien spéciale (bronchitique).

Dans le deuxième groupe, les bacilles de virulence 2 pour le lapin, presque toujours de virulence 2 aussi pour le cobaye, proviennent: deux, de formes très aiguës (dans un cas, le sujet était cachectique du fait du tabes); deux, de formes subaiguës; deux, de formes chroniques.

Dans le troisième groupe, à des bacilles de virulence moindre (3) pour le lapin, correspondent surtout des formes chroniques: il n'y a plus de cas aussi aigus que dans les deux premiers groupes; néanmoins, il est certain que des bacilles d'une virulence égale pour le lapin peuvent se trouver dans des cas d'allure très inégale. Si l'on considère aussi l'activité pour le cobaye, on voit que trois des bacilles de ce groupe sont plus virulents que les autres pour cette espèce. Or, deux sont précisément donnés par les deux cas subaigus; un autre se trouve dans une forme chronique, mais, de même que pour l'exception du premier groupe, il s'agit d'une forme bronchitique. En égard à l'échelle de virulence moyenne, on voit que (le cas de forme bronchitique mis à part) la virulence 2 se trouve dans deux formes subaiguës; la virulence 3.5, dans deux cas chroniques; 3, dans un cas chronique aussi avec poussées aiguës.

Dans le quatrième groupe, c'est encore, en correspondance avec un degré un peu plus faible de virulence pour le lapin, un mélange de cas chronique et subaigus qui, dans leur ensemble, ne diffèrent pas des cas qui correspondent au troisième degré. Si l'on considère la moyenne de virulence à l'égard des deux espèces, on voit que la virulence 3 correspond à deux cas subaigus; 3.5 à un cas subaigu aussi; 4.5 à un cas chronique.

Dans le dernier groupe, il y a une parfaite concordance entre l'activité des bacilles es les cas d'où ils proviennent; les bacilles denués de pouvoir pathogène pour le lapin, et de virulence relativement faible pour le cobaye, proviennent tous de cas chroniques.

Il ressort de là qu'il y a une relation manifeste entre la virulence des bacilles et la rapidité d'évolution des cas. Si l'on considère les degrés extrêmes de l'échelle, la concordance est à peu près parfaite: aux bacilles très virulents correspondent presque toujours des formes très aiguës; aux bacilles de faible activité pour le cobaye et sans action sur le lapin, correspondent toujours des formes très prolongées. Pour les bacilles occupant les degrés intermédiaires de l'échelle de virulence, la concordance est moins rigoureuse, tout en se retrouvant dans nombre de cas; ce sont les cas correspondant au deuxième degré qui sont les plus variés.

En présence de ces faits, l'interprétation la plus simple consiste évidemment à dire que le bacille avec son degré de virulence entre comme facteur important dans le déterminisme de la gravité de l'affection qu'il cause.

Objectera-t-on que ce pourrait être l'inverse, que le degré d'activité du bacille retiré d'un sujet donné est au contraire la conséquence même, soit de l'acuité, soit de la chronicité du cas? Mais il faudrait établir que le bacille de Koch s'exalte en proportion de la réceptivité ou s'attenue en proportion de la résistance; outre que cela n'est pas tout en fait en harmonie avec certains faits empruntés aux règles qui commandent les variations du pouvoir pathogène en général d'un agent infectieux, quelques-uns des cas compris dans notre étude montrent que le bacille peut conserver un haut degré de virulence dans des lésions essentiellement chroniques. Inversement, chez un sujet, les bacilles ayant été isolés à deux reprises, d'abord dans une phase chronique, puis dans une phase présentant un certain caractère d'acuité, la virulence a été trouvée identique: une poussée aiguë n'avait pas exalté le bacille.

L'interprétation la plus simple, considèrant la virulence comme facteur de gravité, comme cause et non comme conséquence, reste donc au moins la plus probable; et nous pensons pouvoir formuler comme suit les enseignements qui se dégagent de notre étude:

L'organisme humain, attaqué par un bacille tuberculeux très actif, subit presque toujours une infection à marche rapide: contre les bacilles, très virulents (du moins reçus en quantité suffisante) il ne sait pas se défendre efficacement.

Sous l'action d'un bacille peu virulent, au contraire, il ne réalise jamais que des infections chroniques.

C'est en présence des bacilles de virulence moyenne que s'accusent les différences individuelles.

En fin de compte, pour expliquer la marche si variable de la tuberculose pulmonaire, il ne suffit pas d'invoquer la résistance individuelle, la prédisposition; il est nécessaire de faire la part la plus large à la virulence du bacille infectant. Et, si l'on songe en outre à l'influence du nombre des bacilles reçus, de la répétition des infections, à l'influence aussi de l'état de l'immunité qui peut succéder à une première atteinte, simulant une résistance initiale, il parait permis de conclure que, en matière d'évolution de la tuberculose pulmonaire, le facteur "virulence" prime le facteur "prédisposition."

A CHAMBER IN WHICH DRIED TUBERCLE BACILLI MAY BE HANDLED WITHOUT DANGER.

By A. Parker Hitchens, M.D.,
Glenolden, Pa.

This chamber was designed to avoid exposure of the operator during certain manipulations with dried bacteria, necessary for the preparation of the so-called new tuberculins.

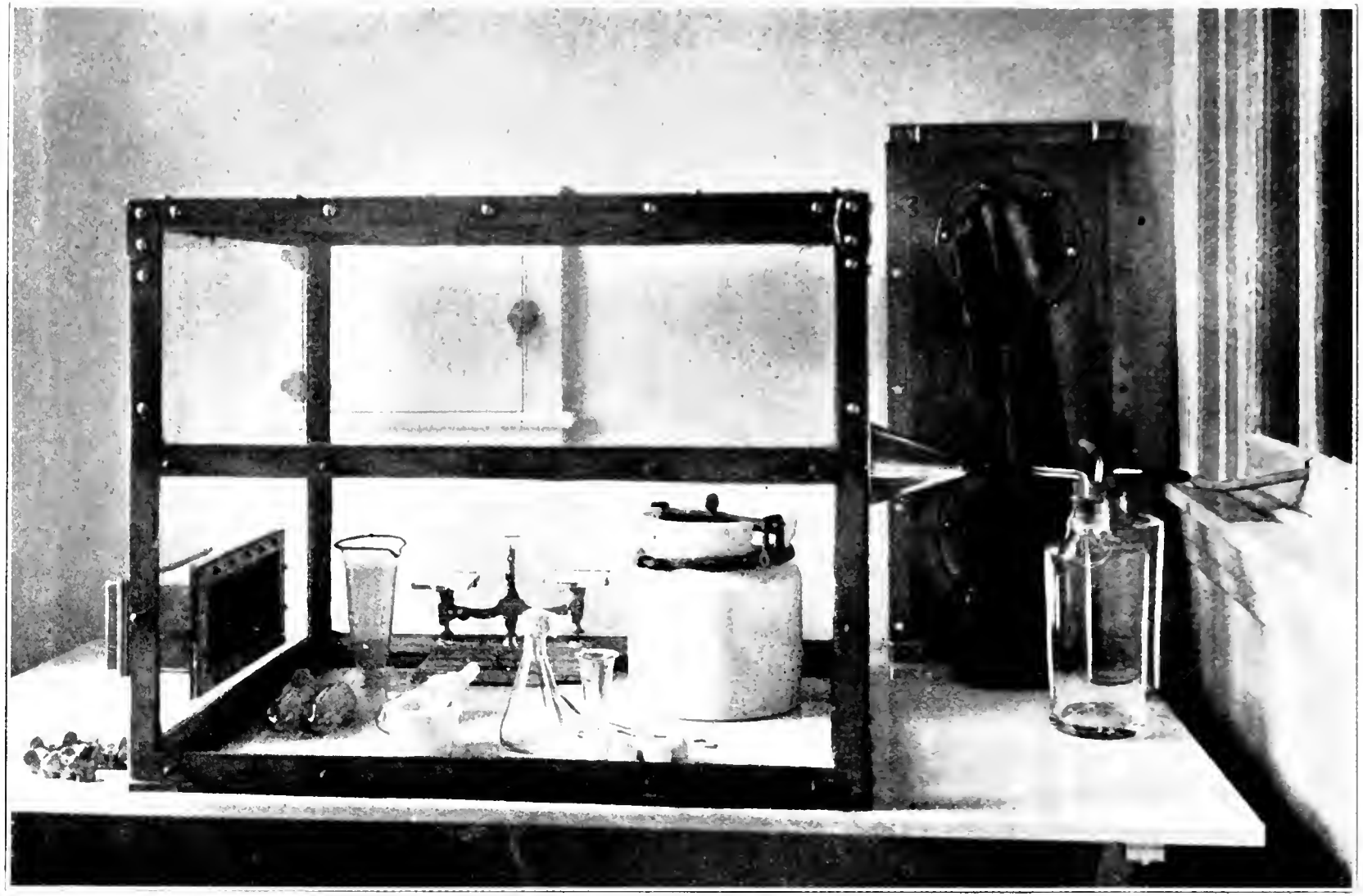
The chamber is 30 inches long, 24 inches deep, and 24 inches high—over all. It has no bottom, but rests upon a very thick, soft-rubber gasket. It is made of heavy plate glass, the frame being brass. The lower half of the front, of reinforced tinned copper, can be removed. This is held in place by bolts and wing-nuts, accurate closure being obtained by the use of a rubber gasket. There are two openings, 6 inches in diameter, in this lower front. These openings have sealed into them rubber gauntlets long enough to permit the hands when inserted into them to reach all parts of the chamber.

At one end of the chamber, near the bottom, is an oblong box, 10 inches long, by 4 inches high, by 4 inches deep. This is open on both sides, except for a fine wire screen at the inner side and a removable lid at the outside. The lid consists merely of a frame and copper gauze. This box is packed with sterile absorbent cotton and serves as an inlet and filter for air. The cotton is packed tightly enough to resist somewhat the entrance of air.

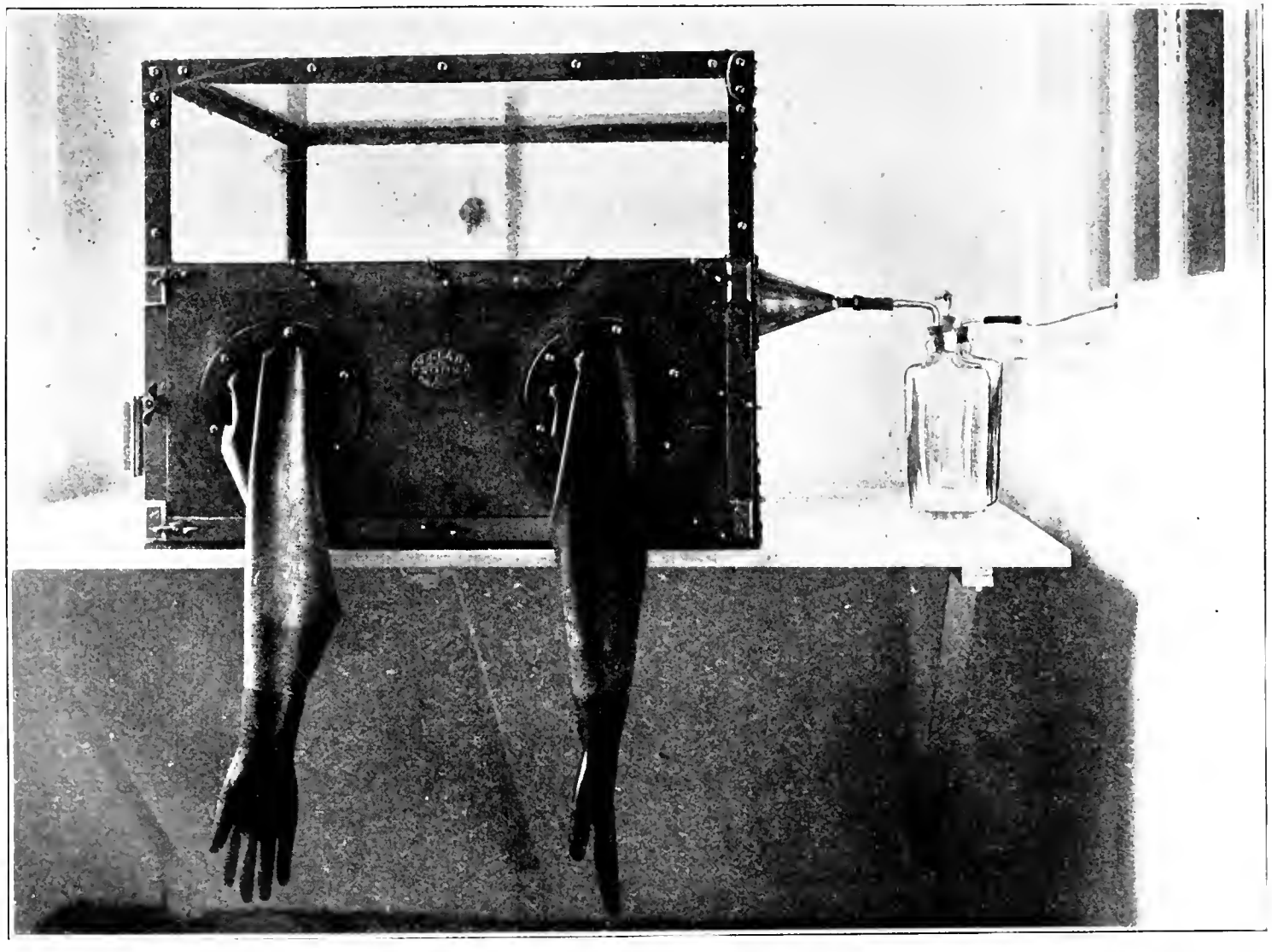
At the other end of the chamber is a funnel, 4 inches in diameter, tapering to about $\frac{1}{2}$ inch. This funnel is attached by means of rubber hose to a vacuum pump, but between the funnel and the pump itself there are two wash-bottles, one containing bichlorid solution, the other containing sulphuric acid.

To use the chamber the lower half of the front is taken off, and all the material and instruments to be used during the operation are put inside; in addition there is placed in a corner, out of the way, a dish of unslaked lime and a quantity of formalin-permanganate, or formalin-magnesium-sulphate mixture.

It is the custom to throw a quantity of some antiseptic fluid into the gloves, so that if it should happen that there is a little opening in one of them, there will be no danger of live germs getting upon the hands.



A chamber in which dried tubercle bacilli may be handled without danger.



A chamber in which dried tubercle bacilli may be handled without danger.

The removable front is then put on and screwed down tightly; the vacuum pump is started—on account of the resistance offered to the entrance of air by the cotton filter there is a slight negative pressure inside the chamber. If it should happen that there are any small cracks about the chamber, air will be drawn in at these openings, thus obviating any danger of the bacillary dust being forced out, when, for instance, the gloved arm is thrust suddenly into the chamber.

After the work has been completed, the product to be kept is sealed up. The formalin mixture is poured upon the lime, and both the vacuum pump and the air-filter box are closed. Sufficient formalin gas is generated to destroy exposed living organisms within the chamber.

The next morning the air-filter is opened and the vacuum pump started in order to remove the formaldehyd before the chamber is opened.

The advantages this chamber has over the usual devices for handling dried masses of virulent organisms are quite obvious. In some laboratories it is customary to use the ordinary hood with a current of air constantly carrying the powdered material away from the operator, but hoods do not always work, and if the old law "what goes up must come down" applies to bacteria, there would seem to be some danger to the immediate neighborhood from such a method.

With the chamber just described the operator is absolutely protected and all the effluent is sterilized. The chamber may be used not only for handling tubercle bacilli, but also for handling dried tuberculin and other dangerous biological or chemical substances. Modifications to suit special requirements readily suggest themselves.

It would seem strange if nothing of the kind has been devised for this purpose heretofore; if it has, however, the writer is ignorant of it.

SECTION I.

Pathology and Bacteriology (*Continued*).

SECOND DAY. MORNING SESSION.

Tuesday, September 29, 1908.

CHANNELS OF INFECTION. PREDISPOSITION.
LATENT INFECTION. HEREDITY.

The Section was called to order by the President, Dr. William H. Welch, at half-past nine.

ON THE CHANNELS OF INFECTION IN PRIMARY PULMONARY TUBERCULOSIS.

By N. Ph. Tendeloo,

Leyden.

Many attempts have been made to determine which are the most frequent channels of infection in pulmonary tuberculosis. All agree that primary aërogenous infection occurs, as well as primary hematogenous, namely, hereditary pulmonary tuberculosis. But while some assert that a primary hematogenous pulmonary tuberculosis may arise by intestinal invasion of bacilli, others deny it, maintaining that a pulmonary tuberculosis of enterogenous origin is always—perhaps with extremely rare exceptions—secondary, and preceded by an intestinal tuberculosis or a tuberculosis of mesenteric lymph-glands.

The relative importance of the possible routes of infection has been studied, in different animals, under varying conditions. It seems, according to some investigations, that the guinea-pig is more easily made tuberculous by aërogenous than by enterogenous infection. But it is very doubtful if the circumstances of human life ever correspond to the conditions of the experiments on animals. So here, as in every other inquiry, experiments with animals show us what is possible,

what must happen under certain circumstances with certain animals, but they can never teach us that it is so in man.

Besides these experiments researches have been made of bacteriological, clinical, social, statistical, and anatomical nature. It is not my intention to speak on them all. I like only to make some remarks.

By bacteriological researches there are found some varieties of Bacillus tuberculosis in human sputa and in human tuberculous tissue. Many investigators maintain that a human pulmonary or other tuberculosis, caused by the so-called "bovine" bacillus, must be of enterogenous origin, as this bacillus must come from cattle, while an infection by the so-called "human" variety may be of different origin.

At first sight this seems rational. But on reflection we find that the premise that the bovine bacillus must come from a cow, and an infection by it must be enterogenous, is not sufficiently supported by experimental and other researches. Even if we should admit that we are able to surely distinguish human and bovine bacilli, the question is not yet answered, how long the bovine bacillus keeps its properties, while growing in human tissue. In other words, it is not proved that the bovine bacillus, if remaining some time (how long?) in human tissue, loses its own properties and takes those of the human variety. The experience that the bovine bacillus is sometimes found in tuberculous human tissue does not show, as some suppose, that this bacillus came from a tuberculous cow into that human tissue. It teaches us, on the contrary, that the bovine bacillus can remain a long time in human tissue, growing in it and making changes in it, without losing its bovine characteristics. Why should it alter these characteristics instantly after entering from a human body into another human body?

The question is not yet answered whether passages through human tissue are able to change the bovine bacillus into the human type; and, if they can, how many passages are necessary for this change? One passage apparently is not sufficient. Without having proved that a second passage through the human body, that is, that the abode in a second human body, always performs in the bovine bacillus the change of the bovine into human characteristics, the premise is wholly arbitrary that bovine bacilli, found in tuberculous human tissue, should have come from a tuberculous cow. Without that proof it seems equally probable that those bacilli came from another tuberculous man, and that this man again was infected by another man, and so on. If tubercle bacilli of the most characteristic bovine type are found in man, it does not follow that the next preceding host of this bacillus must have been a cow. It may have passed through a number of men without losing the bovine characteristics. We have no right to make, without more data, any deduction as to the source of bovine bacilli found in tuberculous human tissue, before we know how many passages through the human body are necessary to change the bovine into human peculiarities.

It will scarcely be possible to determine this, but this difficulty, however great it may be, is not able to alter the postulates of logic.

We must remark here that, even if it were proved that a certain number of passages through bovine body always changed the characteristics of the human bacillus into bovine characteristics, this proof would not at all indicate that as many passages through the *human* body would change the bovine bacillus into the *human* type.

Even if it were sure that the bovine bacillus found in human tissue came last from a cow, it is not yet decided that the infection must be enterogenous. Cows cough and may infect one another by coughing. So also a human being might be infected by inhalation of bovine bacilli floating in the air near a tuberculous cow, apart from other possibilities.

I think that all researches of that kind have not answered the question of the most frequent channel of infection, and that they can never do it.

We must make more direct researches. I mean we must try to examine most closely, on the one hand, the daily social danger of infection of mankind along different channels, as Cornet and Flügge did for aërogenous infection; on the other hand, the first anatomical changes in the human body, comparing them with the experimental results. Such researches are able to answer most accurately the question of the frequency of the different channels of infection.

The question, Which is the most frequent channel of infection in primary pulmonary tuberculosis? is inseparably bound to this question, Where are the first tuberculous changes in human body?

In opposition to the opinion of some authorities, we must accept that an exact complete post-mortem examination in very many cases will show us the channel of infection.

Cornet has shown, with more than 3000 guinea-pigs and rabbits, that, if bacilli are inoculated in widely different spots of the body, the first tuberculous change arises either on the spot of inoculation or in the regionary lymphatic glands. Many other students, though expecting to find another, have obtained the same answer, or, at least, there was no contradiction to Cornet, except some few French experiments. Now, apart from experimental faults, the possibility of exceptions, by anomalies of the lymphatic system, is not to be excluded, though the rule is scarcely weakened by very rare exceptions. We will not take these exceptions into account.

If at post-mortem in a human body only tuberculosis of one or more mesenteric lymph-glands is found, this infection was enterogenous; if only tuberculosis of one or more peribronchial lymphatic glands, the bacilli have reached the gland or glands through the lung, from which organ the peribronchial glands receive their lymph.

So in relation to pulmonary tuberculosis, the seat of the first small

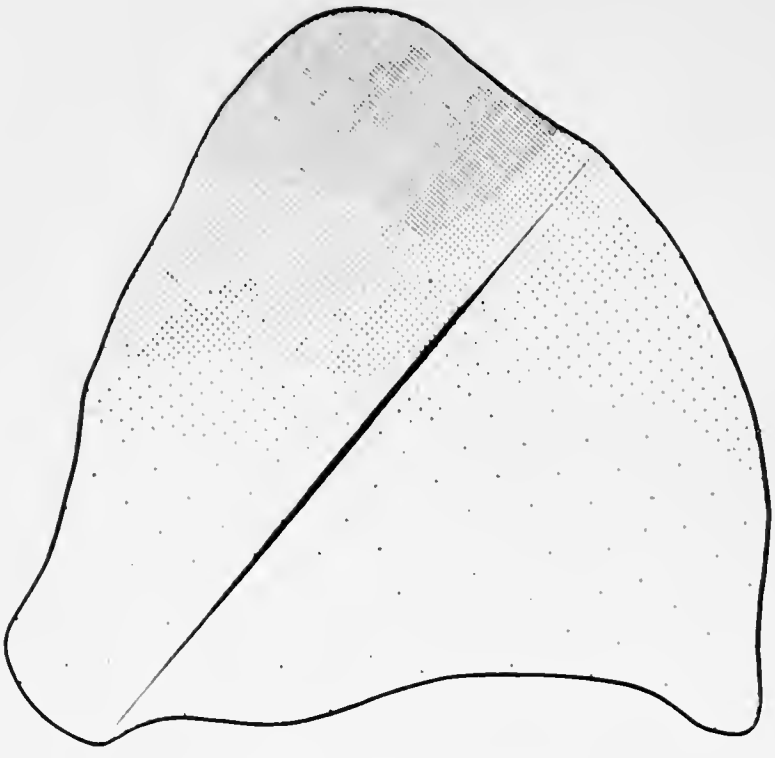


Fig. 1.—Showing in a schematic way the probable location of first foci in primary pulmonary tuberculosis, the highest probability belonging to the paravertebral cranial part of the lung, the probabilities diminishing rapidly in all directions.

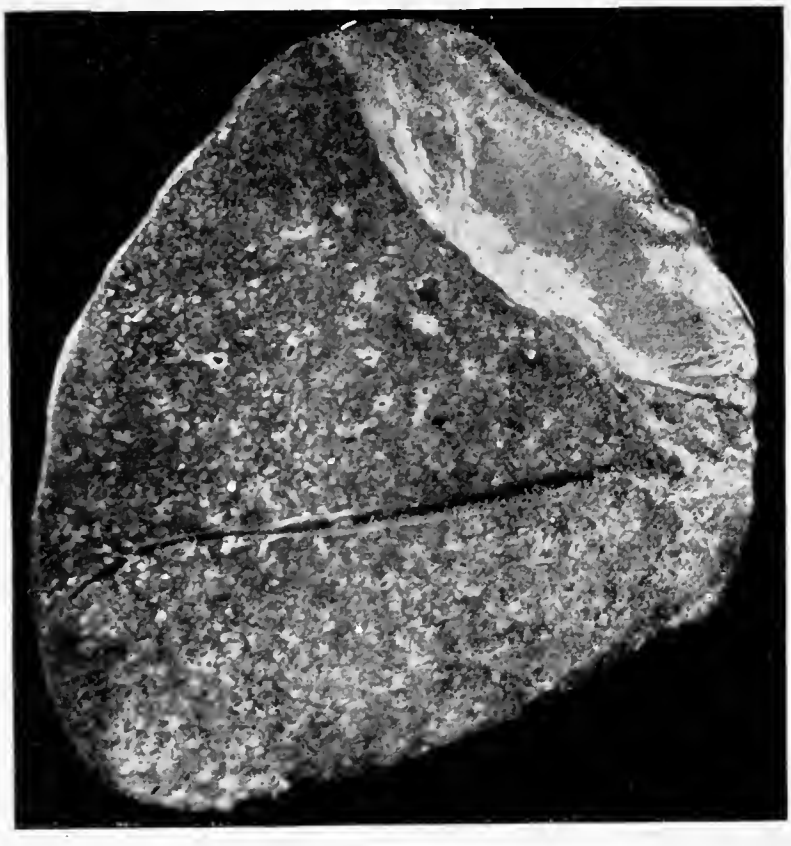


Fig. 2.—Showing uniform distribution of pulmonary tubercles in general miliary tuberculosis.

foci is of great importance. It is indifferent whether there is or is not, at the same time, tuberculosis of bronchial lymphatic glands, since tuberculosis of these glands, without other tuberculous changes in the body, must have been caused by bacilli coming from the lung.

It has been accepted for a long time that pulmonary tuberculosis begins in the apex of that organ. But this is an error that has caused much confusion. All explanations of the primary pulmonary tuberculosis, founded on this error, fall with it, as, for instance, the hypothesis that pulmonary tuberculosis should begin in the apex, since the apical tissue is bloodless.

Nevertheless, the seat of the primary pulmonary foci is of deciding value. I mean recovered, as well as not recovered, latent as well as manifest foci, which we find by post-mortem examination, by inspection, and last, not least, by exact palpation of all the parts of the lungs.

Where do we find them?

A primary tuberculous pulmonary focus often begins in the apex, but also often in other parts of the lung. Little foci may be found in all parts of the lung, but not equally frequently. By far the most foci are found in the paravertebral cranial part of the lung, that is, in a pulmonary sector, close to the vertebral column, cranial from the fifth rib, about between the hilus and the apex, including the apex. From here the frequency of the first foci rapidly diminishes in all directions, as is indicated in Fig. 1. This statement is supported by so many observations that it is not to be doubted.*

The physician who examines but the apex, and not the paravertebral cranial parts of the lung, does not fail again and again to overlook beginning pulmonary tuberculosis. In children a manifest tuberculosis begins more frequently in the central part of the lung than in adults.

That great preference of beginning tuberculosis for certain parts of the lung is of a deciding value for our knowledge about the most frequent channel of infection. If we compare numerous cases of typical general miliary tuberculosis, we find in all parts of the lung equally numerous tubercles, whether the case is acute or chronic. In Fig. 2 we see an instance from nature.

We must remark here that in acute cases sometimes the tubercles in the caudal parts are only to be found by very exact examination, even only microscopically, as they are buried in hyperemic or inflamed tissue, nearly or wholly invisible. I think that this may be a reason why some researchers maintain that general miliary tuberculosis prefers the cranial parts of the lung. Another reason may be this: if there are but few tubercles, they are not always equally disseminated in the lung; in some cases some parts, for

*See my "Studien über die Ursachen der Lungenkrankheiten," Wiesbaden, 1902 (Bergmann), pp. 338 et seq., 417 et seq.

instance, some cranial parts, are preferred. But this phenomenon does not prove that these parts generally are preferred to other parts by hematogenous tuberculosis, as there are other cases where more tubercles are to be seen in caudal than in cranial parts.

On the contrary, all the different cases together, after calculation of chance, show us that hematogenous miliary tubercles do not prefer certain parts of the lung. This is in perfect accord with the experimental results; if we inject into an ear vein of a rabbit very numerous bacilli of Koch, numerous tubercles arise in the lung, equally disseminated.

We conclude: the chance of a hematogenous tubercle is equal in all the parts of the lung. If but one hematogenous tubercle or other embolic tuberculous focus arises in a lung, this focus will be found once in a certain part, in another case in another part, of that organ, and so on. If we collected cases of a single hematogenous embolic tuberculous focus in a lung, as numerous as the miliary tubercles in Fig. 2, and if we marked the seat of all those single foci in one lung, we should obtain a distribution like that of the hematogenous tubercles in Fig. 2.

But if we took as many cases of single tuberculous focus of unknown origin, such as we find by post-mortem examination, and if we marked all these foci in one lung, we should get a distribution very unlike that of the hematogenous tubercles, by far the most foci being in the paravertebral cranial sector, and from that part rapidly diminishing in all directions. Fig. 1 shows us this schematically. In the darkest parts beginning manifest tuberculosis is found. In other words: the preference of primary pulmonary tuberculosis for certain parts of the lung is in open defiance of a hematogenous origin.

Now in chronic general miliary tuberculosis the cranial tubercles are larger than the caudal. But that phenomenon has nothing to do with the localization of hematogenous tubercles, which also in chronic general miliary tuberculosis are equally numerous in all parts of the lung. That phenomenon is due to a slower growth of the tubercles in the caudal parts, which is caused by greater respiratory movements of the lymph in the caudal than in the cranial parts, as we will see directly. For the virus is partly washed away by the circulating lymph as soon as the tubercle has reached a certain size. The greater the movements of the lymph, the more the tubercle is washed out, the less the virus can accumulate, and the slower the growth and the casification are. The opportunity for hematogenous tubercles is equal in all parts of the lung. The opportunity for growth, however, is inversely proportional to the respiratory movements (kinetic energy) of the lymph: it diminishes from the apex in caudal and ventral direction.*

*See my "Studien," pp. 65 et seq.

How can we now explain the preference of primary pulmonary tuberculosis for certain parts of that organ?

If we determine more precisely the seat of the primary tuberculous foci in the lung, we find them most in peribronchial, perivascular tissue, and in the wider parts of the pleural and subpleural lymphatics, or in lymphadenoid tissue, that is, in places where the respiratory movements of the lymph are the slightest. These movements depend on the respiratory movements of the air-vesicles, which are not equal in all parts of the lung: those of the paravertebral cranial vesicles are the slightest, and from here they increase in all directions. That seat of primary pulmonary tuberculosis which is (by far) the most frequent indicates a lymphogenous origin.

To understand this it is necessary to know on what the growth of the bacilli depends.

The question, whether bacilli will grow in a tissue or not, depends on their number and virulence, on the one hand, and on the biochemical properties of the tissue with its humors, on the other hand. Now, the number of the bacilli, and the concentration of the virus in a certain place, depend not only on their original quantity, but also on the movement of the fluid in which they are. The greater this movement (kinetic energy), the less the physical opportunity for settling and accumulation of the virus; consequently the less the physical opportunity for growth of the bacilli and injury of the tissue.

In hematogenous miliary tuberculosis that opportunity apparently in all capillaries is equal, as the bacilli form emboli which in all capillaries seem to arise with equal facility. We can see this also by injecting most minute color-particles in the ear vein of a rabbit. There is apparently no reason to suppose that there are deciding biochemical differences of the pulmonary tissue in the different parts of that organ. In young or old, previously healthy or sick, from all social strata, we see an equal dissemination of the tubercles in general miliary tuberculosis.

As the biochemical properties of the tissue do not show deciding differences, we understand why *lymphogenous* tubercles arise most easily wherever the respiratory movements of the lymph are the slightest. In other words, if we should introduce, at the same time, into all the lymphatics of the lung, the same number of bacilli, beginning with one, and if we should increase the number equally, the first infection would arise in the above-mentioned paravertebral cranial parts. And infection in the other parts should follow the latter, the greater the respiratory movements of the lymph are, for the chance of lymphogenous infection depends on the physical opportunity for arresting and accumulating the virus; that is, that chance is inversely proportional to the respiratory movements of the lymph.

For this reason in caudal pulmonary tissue a tuberculous focus develops from a larger quantity of virus than is required in cranial tissue, a quantity such as may be imported into caudal bronchi from a cranial cavity. Then an acute tuberculous process of large extent may develop in caudal tissue. Such a quantity of virus is extremely seldom inhaled by man.

For the same reason a paralytic thorax increases the physical opportunity for lymphogenous infection in the cranial pulmonary tissue, as in that form of chest the respiratory movements of that tissue are slighter. For that reason, also, every formation of connective tissue which does not lead to obliteration of the lymphatics is able to increase the physical opportunity for lymphogenous infection. Just as in new-formed tissue more dust-pigment accumulates, as we see in slate-colored induration, so bacilli accumulate more easily.

The influence of the respiratory movements of the lymph is also to be seen in the rapidity of growth of a tuberculous focus, as we remarked above in regard to chronic miliary tuberculosis. This is one of the reasons why generally caudal bronchopneumonic foci are smaller than cranial.

It may be asked why non-tuberculous, especially acute, infections are found in caudal parts of the lung. We cannot dwell here any longer on the channel of infection in those inflammations, but we must confine ourselves to these remarks: If we consider only those non-tuberculous infections which are broncholymphogenous, as, for instance, the common fibrinous pneumonia, there is but this difference: the bacillus of Koch grows very slowly—about ten to twelve times slower than the bacteria which cause the non-tuberculous inflammations. The formation and accumulation by growth of tuberculous virus come on more slowly than occurs with other bacteria. So the physical opportunity for accumulation of virus is less for rapidly growing bacteria than for the Bacillus tuberculosis. The former grow better in hyperemic than in bloodless tissue, as experiments have taught, and therefore better in caudal than in cranial pulmonary tissue. Besides, in most cases these infections are secondary, that is, preceded by an injury of the pulmonary tissue, which makes this tissue, peculiarly caudal tissue, hyperemic.

But if we believe that primary pulmonary tuberculosis almost always is lymphogenous, we have still to answer the question: Whence and how do the bacilli come into the lymphatics of the lung?

Experimental researches have shown that hematogenous tuberculous foci develop as emboli; that the bacilli do not leave the capillaries to enter into the lymphatics. But there are three other possibilities: (1) The bacilli might come from abdominal lymphatics; (2) the bacilli might come from cervical lymphatics; (3) the bacilli might come from the inhaled air in the bronchi and air-vesicles.

As to the first possibility, it is not to be accepted that the bacilli are carried from the intestines into mesenteric, and from these into pulmonary, lymphatics. There could be no question about other abdominal lymphatics. We must not forget that cases of primary tuberculosis of an abdominal organ, and consequently of secondary pulmonary tuberculosis, are excluded here. But even if there came bacilli from the abdominal into pulmonary lymphatics, it were dubious whether these bacilli would reach the cranial lymphatics. Taking all together, we must reject this first possibility.

Secondly, it is possible that bacilli came from the cervical into the pulmonary lymphatics, either directly or after having infected one or more peribronchial lymphatic glands, and then from these glands, by retrograde movement of the lymph, into the pulmonary lymphatics.

In both cases it is not to be admitted that bacilli would travel from the cervical into intrathoracic lymphatics without passing, that is, without changing, any cervical lymphatic gland. In other words, even if we should accept one or both possibilities of lymphogenous infection of the lung from the cervical lymphatics, we could only admit them for those cases where tuberculosis of cervical lymphatic glands exists. In such cases, however, the pulmonary tuberculosis would be secondary.

But may it not be true that in many cases the pulmonary tuberculosis, apparently primary, is really secondary, following on a cervical tuberculosis? A tuberculosis of cervical lymphatic glands will not easily be overlooked by an exact post-mortem examination. And in adults it is but rarely found. Now we will consider the third possibility.

It has been proved by numerous experiments (Cornet, Flügge, etc.) that bacteria floating in the air, either in dry dust particles, or suspended in minute fluid particles, may be inhaled into the bronchi, bronchioli, and air-vesicles, where they fall down, just like inhaled dust particles. In the air-vesicles they may be taken up by the tissue and pass into the lymphatics, just as inhaled dust particles. Then they are driven away by the lymph, and they settle in parts of the lung where the movement of the lymph offers opportunity for it—that is, where that movement is not too fast. The rest of the bacteria or particles are carried into the pleural or subpleural tissue or the peribronchial lymphatic glands.

If the inhalation of minute particles floating in the air gave an equal precipitation of them in all the air-vesicles of the lung, they would, after arriving in the lymphatics, accumulate most in the paravertebral cranial tissue, especially in the peribronchial, perivascular, pleural, and subpleural tissue, that is, just in the same places, where by far the most primary tuberculous foci are found. The more the lymphogenous accumulation in these parts is favored, so the precipitation of these floating particles in

the paravertebral cranial bronchi and air-vesicles surpasses that in other localities.*

So the experience is to be explained that primary tuberculous bronchitis is found in paravertebral cranial bronchi.

Sometimes the form of the focus indicates a bronchogenous, also an aërogenous, origin. I mean the bunches which tubercles may form, just as in bronchogenous metastases and primary bronchopneumonic foci.

It is not impossible that sometimes pulmonary tuberculosis is caused by virus, drawn in or flowing in from the mouth or throat. But in such a case the focus is to be expected in the center of the lung, near the hilus. It might occur, but as a rare exception.

We are led to the conclusion that primary pulmonary tuberculosis, in by far the most cases, is of *aërolymphogenous origin.*

A beginning focus, under certain circumstances, may develop into any form of pulmonary tuberculosis. But we must not lose sight of this: however important the scientific examination of the frequency of the different channels of infection may be, it is indifferent, from a social point of view, whether pulmonary tuberculosis is enterogenous or of bovine origin in 5 or 15 or even, if it were so, in 30 per cent. of cases. The main thing is, that there is an enterogenous tuberculosis, which may be of human or bovine origin, and there is a traumatic human as well as bovine tuberculosis, and there is a hereditary, and there is an aërogenous tuberculosis. We have to exert ourselves to the utmost to prevent all these infections.

*"Studien," pp. 92 et seq.

ZUR FRAGE DER INFEKTIONSWEGE DER TUBERKULOSE.

Von Julius Bartel,
Wien.

Es kann nicht meine Aufgabe sein, bei dieser Gelegenheit in eingehender Weise den Entwicklungsgang der Eintrittspfortenfrage bei der Tuberkulose zu erörtern, nachdem dieses ja namentlich in den letzten Jahren auf den verschiedenen Kongressen und in zahlreichen Arbeiten von berufener Seite in ausführlicher Weise geschehen ist. So will ich mich mit einem kurzen Rückblick begnügen und dann sofort an das Referat meines Chefs, des Herrn Prof. Weichselbaum, auf der VI. Internationalen Tuberkulose-Konferenz in Wien im Jahre 1907 und meine bei dieser Gelegenheit veröffentlichten Leitsätze anknüpfen.

Wir wissen, dass schon in der Zeit vor Kochs epochaler Entdeckung die Eintrittspfortenfrage lebhaft erörtert, Gegenstand des Widerstreites war. Ich erinnere nur an Klebs, v. Bollinger, und Orth, dessen damaliger Hinweis auf eine "Latenz" der Tuberkulose mir bemerkenswert erscheint, wenngleich der damalige Stand der Erkenntnisse noch keinen weiteren Ausbau dieser Frage gestattete. Mit Kochs Entdeckung hebt ein Zeitraum an, in welchem die Anschauung von der ausschliesslichen oder fast ausschliesslichen Inhalationsinfektion fast zur allgemeinen Geltung kam. Von Koch selbst betont, von Cornet auf Grund des "Lokalisationsgesetzes" mit grösster Schärfe vertreten, von Flügge durch zahlreiche eingehende Experimente gestützt, schien es natürlich, dass auch fast alle Kliniker sich diese Anschauung zu eigen machten, umso mehr als der Obduktionsbefund mit der so überaus häufigen, vorherrschenden und auch isolierten Tuberkulose von Bronchiallymphdrüsen und Lungen einwandfrei die Kette der Beweise zu schliessen schien. Und gerade von pathologisch-anatomischer Seite, von Orth, fällt in diese Zeit der Hinweis auch auf die Bedeutung einer metastatischen Lokalisation, besonders im Bereiche der so häufig erkrankten Lungen. Fast als eine natürliche Reaktion erscheint es mir, wenn dann, ausgelöst durch die bekannten Ausführungen v. Behrings, sich zahlreiche Stimmen erhoben, welche mehr oder weniger apodiktisch auf die grosse Bedeutung auch der Fütterungs-Infektion hinwiesen. Uns sind ja die Anschauungen von Calmette, Schlossmann, der Schüler von Heller und Hueppe, von Kovacs, von Ravenel bekannt.

In dieser Zeit nun hat Weichselbaum in seinem Institute in Wien die Inangriffnahme der Tuberkulosefrage überhaupt und im Speziellen der Eintrittspfortenfrage angeregt, und haben jene Arbeiten ihren Anfang genommen, über deren Ergebnisse ich jetzt berichten will. Sie wurden von Weichselbaum und mir, von mir allein, und mit Hilfe meiner Mitarbeiter, Bachrach, Hartl, Herrmann, Neumann, Spieler, und Stein durchgeführt und grösstenteils bereits veröffentlicht.

Als zunächst erwähnenswertes Ergebnis dieser Untersuchungen verzeichne ich den Nachweis einer "Latenz von Tuberkelbazillen in anscheinend unveränderten Organen, speziell in Lymphdrüsen," welcher Nachweis mir im Fütterungsexperiment am Kaninchen gelang und den Weichselbaum und ich in Übereinstimmung mit den früheren und späteren Befunden von Kälble, Macfadyen und Macconcey, Harbitz, Rosenberger, Ipsen, Goodale, Rabinowitsch, Weber und Baginsky, Gaffky und Hess, sowie Calmette auch für den Menschen erbrachten. Im Tierexperiment gelang mir ferner der Nachweis, dass eine solche Latenz auch von längerer Dauer sein könne und haben Weichselbaum und ich dieses auch für den Menschen als wahrscheinlich angenommen. Mikroskopisch liessen Lymphdrüsen in diesem Stadium der Tuberkulose lediglich mehr oder weniger ausgeprägte hyperplastische Wucherung der Lymphozyten erkennen oder waren "anscheinend" unverändert, zeigten also für eine Diagnose auf Tuberkulose durchaus uncharakteristische Bilder. Ich bezeichnete diese Tuberkuloseform als "lymphoide Tuberkulose"—und zwar weniger in des Wortes etymologischer Bedeutung, als im Sinne einer durch eingewanderte Tuberkelbazillen hervorgerufenen allerdings uncharakteristischen Veränderung, resp. eines gleicherweise bedingten Zustandes, wie ja ein ähnlicher Sprachgebrauch schon bezüglich der pyogenen Infektion herrscht. Dabei stellte ich die "lymphoide Tuberkulose" als erstes Stadium der "manifesten" Tuberkulose, d. i. der spezifischen Tuberkelbildung als dem Endstadium gegenüber, wie Cornet nach Virchow bei der pyogenen "Scrofulose" der Lymphdrüsen das erste "hyperplastische" Stadium vom Endstadium, dem Abszess unterschied, für die tuberkulöse Scrofulose allerdings lediglich die Entwicklung des spezifischen Tuberkels, die "manifeste" Tuberkulose anerkannt wissen wollte.

Weitere Beobachtungen einer Ausheilungsmöglichkeit der Tuberkulose im Stadium lymphoider Latenz führte naturgemäss zur Erkenntnis der "Schutzwirkung speziell des lymphatischen Gewebes gegenüber einer tuberkulösen Infektion," in dem es in der Folge gelang, eine die Virulenz von Tuberkelbazillen (Typus humanus und bovinus) abschwächende und schliesslich auch aufhebende Wirkung des lymphatischen Gewebes und dann auch anderer Organe und aus solchen bereiteter Stoffe zu erweisen. Auf dieser Grundlage wurden nun mehr "Immunisierungsversuche" in mannigfacher

Variation von Immunität und virulenter Infektion aufgebaut, welche folgende Resultate ergaben:

"Überempfindlichkeit wie erhöhte Resistenz und endlich auch volle Immunität gegen eine virulente Infektion;

"Ausheilungsvorgänge in manifest tuberkulös veränderten Organen-Cirrhose der Leber, Bindegewebsneubildung in Impfinfiltraten, Lymphdrüsen, und Lungen;

"Vorherrschende manifeste Tuberkulose der Lungen bei erhöhter Resistenz wie bei Überempfindlichkeit gegenüber virulenter Infektion;

"Auch die isolierte manifeste Tuberkulose der Lungen bei metastatischer Infektion von entfernt gelegener, anscheinend unveränderter Eintrittspforte, sowie auch unveränderten regionären lymphatischen Apparat der letzteren bei Ausschluss jeder Gelegenheit zur direkten Lungeninfektion;

"Manifeste Tuberkulose infolge Überempfindlichkeit bei bestimmter Art der Infektion ohne manifeste Tuberkulose des zur Kontrolle in gleicher Weise infizierten Tieres."

So lehrt uns das Experiment bei Beachtung der Beziehung von Immunität und virulenter Infektion, wie auch der Befund manifester Tuberkulose eines speziell disponierten Organes ohne Kenntnis des Werdeganges des Erkrankungsprozesses nicht so apodiktisch sicher zur Bestimmung der Eintrittspforten, namentlich im Einzelfalle herangezogen werden kann, also auch die Tuberkulose, wenigstens beim Tier, unter gewissen Umständen den Charakter der "kryptogenetischen" Infektion tragen kann.

Auf anderen Wegen gelangten Askanazy, v. Behring, Bongert, Orth, und Weber in mancher Hinsicht zu ähnlichen Beobachtungen, wie Form und Ausbreitung der Tuberkulose bei wechselnder Beziehung von Disposition, Immunität, und Virulenz mannigfache Änderung erfährt. Für die "Verhältnisse der Humanpathologie" erscheinen mir diese Beobachtungen sehr wertvoll, da sie nach der Anordnung des Experimentes weit eher geeignet sind, eine verlässliche Vergleichsbasis für die Beurteilung der Entstehung und der Formen, sowie des Verlaufes der menschlichen Tuberkulose zu schaffen, als die hiezu wohl weniger geeigneten Impfversuche mit virulenten Kulturen an normalen Versuchstieren, namentlich dem für die Tuberkulose-Infektion jeder Art so empfindlichen Meerschweinchen. Und gerade Versuche letztgenannter Art waren es ja, welche die Grundlage des "Lokalisationsgesetzes" in seiner starren Form abgegeben haben, wie es Cornet aufgestellt hat, Ribbert ohne Einschränkung angewendet wissen will. Erwägen wir unsere Kenntnisse über Vorgänge natürlicher Immunität, wie wir sie wohl schon als Gemeingut betrachten können, und ziehen wir den Vergleich mit dem Resultate der Kombination von künstlicher Immunität und virulenter Reinfektion im Experiment am Tier, dann gelangen wir

auch für den Menschen ohne Zwang zu ähnlichen Vorstellungen. Dabei können wir mannigfache Möglichkeiten in Erwägung ziehen:

"Intrauterine Infektion mit Manifestation des Krankheitsprozesses schon zur Zeit der Geburt oder lymphoide Latenz mit manifest tuberkulöser Erkrankung auf Basis der intrauterinen Infektion erst im späteren Alter, eventuell über die Zeit der Kindheit und die zweite Wachstumsperiode hinaus.

"Postfetale Infektion mit rasch anschliessender Manifestation der Tuberkulose oder gleichfalls längere lymphoide Latenz mit erst später aus dieser sich entwickelnder Bildung typischer Tuberkel.

"Ablaufen der intrauterinen oder postfetalen Infektion schon im Stadium der lymphoiden Tuberkulose mit Auslösung von Immunitätserscheinungen; in verschiedener Zeit nachher Reinfektion: entweder mit manifester Tuberkulose, variabler Extensität und Intensität, sowie verschieden raschen Ablauf der Entwicklung und Rückbildung, oder mit Freibleiben von jeder spezifisch tuberkulösen Erkrankung. Bei Vorhandensein von Überempfindlichkeit und erhöhter Resistenz, Neigung speziell disponierter Organe zu manifester Tuberkulose, sowohl für die primäre als auch für die metastatische Infektion, auch wenn die entfernt gelegene Eintrittspforte mit ihrem regionären lymphatischen Apparat nicht spezifisch tuberkulös verändert erscheint."

Mit den von Orth niedergelegten Anschauungen, noch mehr mit den Ansichten, die v. Behring und v. Baumgarten vertreten, finden wir hier mannigfache Berührungspunkte und setzen namentlich die Meinungen der beiden letztgenannten Autoren ja gerade eine Latenz im "anscheinend" unveränderten Gewebe voraus.

Wenn ferner im "Fütterungs- und Inhalationsexperiment am Tier" die verschiedenen Autoren übereinstimmend die Überlegenheit der Inhalationsinfektion bezüglich einer rasch und sicher entstehenden manifesten Tuberkulose beobachtet haben, so ist dieses Resultat zunächst nur ein Zeichen der besonderen Empfänglichkeit der Lungen für die direkte Infektion durch Inhalation, wie ja die spezielle Disposition des genannten Organes für die metastatische Infektion, also ohne direkten Import des Erregers, bereits als feststehend angesehen werden muss. So erscheinen mir auch Findels Ermittlungen, dass 63 per Tracheam inhalierte Bazillen rasch und sicher zur manifesten Tuberkulose führen, zu einem positiven Resultat im Fütterungsexperiment die 6,000,000-fache Menge erforderlich ist, in erster Linie auch nur als Beweis einer speziellen Disposition der Lungen als des so häufig erkrankten Organes.

Der Nachweis ferner von Tuberkelbazillen in den Lungen kurz nach experimenteller Inhalationsinfektion auf natürlichem Wege durch Neumann und mich, wie die Befunde von Hartl und Herrmann im Einklang mit den

Angaben früherer Autoren, widerlegten zunächst nur die Anschauung, nach der ein Eindringen von Krankheitserregern auf direktem Wege per Inhalationen bis in die Lunge unmöglich ist. Wollen wir aber auf die Bedingungen, wie sie "die natürlichen Infektionsverhältnisse" schaffen, aus diesen Beobachtungen bei künstlicher Infektion einen Rückschluss ziehen, so kann dieses wohl nur mit ganz besonderer Vorsicht geschehen. Mit Spieler habe ich gesunde Meerschweinchen in einer Phthisikerwohnung den daselbst obwaltenden Infektionsgelegenheiten ausgesetzt und dann mit Beachtung der lymphoiden Tuberkulose die Verhältnisse der natürlichen Infektion studiert. Wenn ein viertägiger Aufenthalt in der Wohnung genügte, eine allerdings erst nach 184 Tagen tötliche chronische Mesenterialdrüsentuberkulose mit allgemeiner miliarer Aussaat zu erzielen, so müssen wohl hiebei unzählbare Tuberkelbazillen in den Darm gelangt, aber weniger als 63 Tuberkelbazillen nach Findel direkt in die Lunge inhaliert oder aspiriert worden sein. Trat ferner erst bei siebenmal so langem Aufenthalt in der Wohnung eine chronische Lungentuberkulose auf, welche dann allerdings die Mesenterialdrüsentuberkulose an Intensität überholte, so muss man wohl zum Schlusse gelangen, dass eine direkte Übertragung einer rein experimentellen Fütterungs- oder Inhalationsinfektion auf die Verhältnisse des praktischen Lebens nur mit grösster Vorsicht und Reserve gestattet ist.

Jedenfalls kann man aus allen den angeführten Beobachtungen sehen, wie schwierig und unsicher ein Urteil über die Eintrittspforten, namentlich im Einzelfalle, sich gestalten kann, besonders wenn sich ein solches Urteil lediglich auf den Nachweis manifester Tuberkulose auf dem Obduktionstische stützt, also bei der fast stets unbekannten Geschichte des Falles nur ein Endresultat desselben ins Auge gefasst wird. Daher erscheint es mir auch begründet, wenn Weichselbaum und ich seinerzeit auch auf die Notwendigkeit des Nachweises der lymphoiden Tuberkulose hingewiesen haben, wo sicherlich nur vollständige Untersuchungen zu weitergehenden Schlüssen eine Berechtigung geben können. Weichselbaum gelangte auf dieser Basis auch in seinem letzten Referate zum Schlusse, dass, wenn auch die von v. Behring aufgerollte Streitfrage noch nicht entschieden ist, "wir aber schon jetzt behaupten können, die Fütterungs- bezw. Deglutitionstuberkulose komme bei Menschen, besonders im Kindesalter, viel häufiger vor, als bis vor kurzem die meisten Forscher geglaubt haben."

In so manchen Äusserungen aus letzter Zeit finden wir nun tatsächlich eine gewisse Annäherung der gegensätzlichen Anschauungen. Sollte man auch auf Grund der angeführten Momente zur Anschauung gelangen, dass die Unsicherheit des Schlusses in der Eintrittspfortenfrage nunmehr eine noch grössere sei, so kann ich darin einen Nachteil nicht so ohne weiteres erblicken. Jedenfalls tritt die Bedeutung des Widerstreites über den Modus der Infektion im Einzelfall—ob Fütterung oder ob Inhalation wegen des

oft nicht bestimmbaren Effektes infolge Aspiration resp. Deglutition—weit zurück gegenüber der Bedeutung allgemein hygienischer Massnahmen, welche ja auf alle Infektionsmöglichkeiten Bedacht nehmen müssen.

Routes of Infection in Tuberculosis.—(BARTEL.)

In animals we are able to demonstrate in the lymph-glands, in addition to the manifest tuberculosis with specific tuberculous changes, a stage of "lymphoid" tuberculosis in which the glands show mainly lymphocytic hyperplasia or are apparently "unchanged." The existence of such a "lymphoid" stage can be demonstrated in man also.

Attempts at immunization, performed according to the observation of a possibility of a cure of the tuberculous infection in the "lymphoid" stage, gave in combination with reinfection the following results:

"Signs of increased tendency toward, then of increased resistance, and finally of complete immunity.

"Processes of complete cure in organs afflicted with 'manifest' tuberculous changes.

"Mainly 'manifest' tuberculosis of the lungs with the bronchial lymph-glands and cavities in the lungs.

"But also isolated 'manifest' tuberculous disease of the lungs, the portals of entrance remaining perfectly intact and all opportunity of direct lung infection being excluded."

Under certain conditions, therefore, tuberculosis bears the character of a "cryptogenetic" infection.

A similar condition we must also expect in the domain of human pathology according to the laws of natural immunity. Therefore if we only consider the signs of "manifest tuberculosis" during a post-mortem examination, we do not have sufficient to act as a reliable basis upon which to judge the portal of entrance; we must also consider the signs of "lymphoid tuberculosis." As far as we can judge at this time, the infection from pharynx, stomach, and intestines is far more frequent, particularly during early life, than has generally been considered. Of less importance as compared with general hygienic regulations is the constant dispute concerning the more frequent mode of infection, whether due to swallowing or inhalation, inasmuch as it is difficult to judge the relative effects of deglutition and aspiration.

After Dr. Bartel's paper the President of the Section, Dr. Welch, requested Dr. Joseph Denys, of Louvain, Honorary President of the Section, to take the chair. Professor Denys presided during the two discussions next following.

ÉTUDE EXPERIMENTALE DE LA TRANSMISSIBILITÉ DE LA TUBERCULOSE PAR LES CRACHATS DESSÉCHÉS.

Par G. Kuss,
Médecin du Sanatorium d'Angicourt, France.

Le danger de contagion tuberculeuse par les crachats desséchés, affirmé par Villemin en 1869, affirmé de nouveau par R. Koch, démontré par Cornet, Straus, Nocard, admis avec restrictions par C. Flügge a eté contesté et meme nié par Petersson (1900), par Cadéac (1905), par Calmette (1906). Ces trois auteurs ont fait inhaler à des cobayes des quantités formidables de poussières tuberculeuses dessecheés et ont constaté que la plupart de leurs animaux d'expérience restaient indemnés. A la Conference de Vienne on a pu affirmé sans soulever de protestations "qu'il est trés difficile de donner la Tuberculose aux animaux en leur faisant respirer des poussières infectants séches."

Ces rèsultats experimentaux sont-ils exacts? Les crachats de phtisiques, desséchés dans les conditions naturelles peuvent-ils étre considerés comme une source importante de contagion bacillaire? Telles sont les deux questions dont nous avons abordè l'etude experimentale, en les analysant dans leurs éléments fondamentaux.

1. Pendant combien de temps, les crachats tuberculeuse desséchés conservent-ils leur virulence?

J'ai étudié les variations de virulence de crachats tuberculeux étalés en couche mince sur des surfaces lisses (0.20 gr. de crachats frais sur une surface de 1 cent. carré), ou sur des surfaces absorbantes (tapis de moquette, molletons de laine) et abandonnés á l'air libre, soit à l'obscurite, soit à une faible lumière diffuse, soit à la lumière diffuse franche d'une pièce bien éclairée

Voici les principaux rèsultats obtenus.

A. *Les crachats tubercuIeux, desséchés en couche mince à l'obscurité,* à l'air libre, ont, au bout de 12 à 14 jours, une virulence à peu près intégralement conservée.

Au bout de 18 jours, la virulence est diminuée dans une faible mesure; le plus souvent, à cette période, elle demeure encore considérable.

Du 20e au 30e jour, la diminution de virulence s'accentue beaucoup, au 30e jour, la virulence n'est pas encore abolie, mais elle est devenue faible;

dans bien des cas, cependant, avec des doses élevées, on parvient encore à tuer le cobaye en trois à quatre mois avec des lésions de tuberculose miliaire généralisée. A partir du 40–45e jour, on constate généralement la disparition de la virulence.

B. *Les crachats tuberculeux, desséchés en couche mince à la lumière diffuse d'une chambre*, subissent rapidement une diminution de virulence, déjà existante au 3e jour, plus marquée au 7e jour, bien qu'à cette époque on détermine encore, chez le cobaye, des tuberculoses généralisées à évolution assez rapide.

A partir du 10e jour, la baisse de virulence s'accentue dans une notable proportion, variable suivant les cas: la virulence n'est pas complètement perdue au 15e jour, mais au 20e jour elle est nulle.

2. Au bout de combien de temps, les crachats dessechés sont-ils aptes à être reduits en poussières fines? Ces poussières sont-elles virulentes?

La durée de dessiccation nécessaire pour que les crachats puissent être facilement pulvérisés est extrêmement variable: elle dépend de la nature de la surface sur laquelle les crachats sont deposés, de la température et de l'humidité ambiantes, de l'epaisseur des crachats, etc., puis, la dessiccation une fois obtenue, la facilité de pulvérisation est entièrement subordonné a l'état hygrométrique actuel.

Duex notions capitales doivent être retenues:

A. Quand les conditions de dessiccation sont favorables, les crachats se desséchent rapidement, en quelques jours, et se reduisent avec facilité en poussières fines, en particulier par le balayage et par le brossage.

B. Il est absolument erroné de pretendu, comme la fait Cadéac, que les poussières très mobilisables de crachats tuberculeux sont nécessairement des poussières inertes. Les crachats tuberculeux abandonnés à la dessiccation dans un endroit peu éclairé conservent une virulence considérable au moment où ils sont devenus suffisamment secs pour être facilement réduits en poussières fines.

3. Est il facile de tuberculiser les animaux en leur faisant respirer des poussières virulentes obtenues par la pulvérisation artificielle des crachats desséchés?

J'ai fait respirer des cobayes dans une caisse de 152 litres de capacité, dans laquelle je projetais, à l'aide d'un pulvérisateur, la poussière obtenue par trituration (au Martin) de crachats tuberculeux, desséchés à l'obscurité pendant 6 jours.

Les inhalations étaient d'une durée de 30 a 60 minutes; dans chaque expérience, on pulvérisait en totalité 1 à 2 gm. de crachats desséchés, en ayant soin d'éviter toute pulvérisation directe sur les animaux. Dans tous les cas, les cobayes se sont rapidement tuberculisés par inhalation. On ne saurait expliquer autrement que par des erreurs expérimentales les résultats

Fig. 1.—Dispositif adopté pour l'expérience de balayage.

Fig. 2.—Appareil respiratoire du Dr. Tissot qui a servi à l'expérience et qui est appelé à rendre les plus grands services dans les désinfections en raison de la protection parfaite qu'il donne aux opérateurs.

negatifs obtenus dans des expériences similaires par Petersson, par Cadéac, par Calmette: comme l'avait affirmé Cornet, il est extrêmement facile de tuberculiser les animaux avec des poussières séches, par voie d'inhalation.

Mais les expériences faites dans de telles conditions, avec des crachats artificiellement pulvérisés n'offrent qu'un intérêt médiocre au point de vue des conditions de la contagion naturelle.

4. Est il facile de tuberculiser les animaux en les exposant aux poussières dues au balayagé de crachats tuberculeux desséchés.

Mes expériences ont été faites d'une part dans une caisse d'inhalations de 152 litres, d'autre part dans une chambre de 30 mètres cubes.

A. Expériences dans une caisse d'inhalations par brossage de tissus contaminés.

La paroi inférieure de la caisse était recouverte d'un tissu epais de molleton, arrosé de crachats tuberculeux et abandonné à la dessiccation naturelle a l'obscurité pendant 4, 7, 10, 16 jours.

Le brossage avait lieu a l'aide de brosses actionnées de l'extérieur (brosses de fil d'acier et brosses de chiendent).

Les animaux étaient placés en dehors de la caisse, la tête seule faisant saillée à l'intérieur à une hauteur de 32 centimètres au-dessus de la paroi inférieure.

Chaque expérience compartait une seule séance d'inhalation de la 3 heures, au cours de laquelle on brossait a plusieurs reprises le tapis de molleton.

Tous ces cobayes se sont tuberculisés par inhalation: il n'est donc pas douteux que le simple balayage ou brossage de tapis contaminés suffit pour projeter dans l'air, au cours du balayage, des poussières virulentes suffisamment fines et suffisamment légères pour etre aspirées dans les voies respiratoires très étroites des cobayes.

B. Expériences dans une chambre de 30 métres cubes.

Aux expériences d'inhalations précédentes, qui exposaient les animaux a une infection respiratoire très sévere, j'ai superposé une expérience analogue a l'expérience bien connu de Cornet (Balayage d'un tapis contaminé).

Toutefois il faut observer que Cornet s'était placé dans des conditions très spéciales, qui ne sont jamais realisées dans la pratique: sécheresse exceptionnelle de l'atmosphère (E = 31 a 36%), precocité excessive des premières séances de balayage (2e et 4e jours), exposition des animaux accumulés dans une caisse à la projection directe, par le balayage, des particules virulentes. Dispositif expérimental. Les crachats, repandus sur une planche et sur deux tapis, ont été abandonnés a la dessiccation pendant 17, 12 et 6 jours. La température de la chambre a varié de 15° a 25°, l'état hygrométrique de 88 a 60%: aucours de la séance de balayage, la température était de 23°, l'humidité relative de 70%. Pendant les 12 premiers

jours, la chambre est restée dans l'obscurité, pendant les 5 derniers, elle a été exposée a une faible lumiére diffuse.

Les cobayes etaient disposés en divers points d'une surface murale de 3 métres de largeur à des hauteurs audessus du sol variant de 75 a 175 centimétres.

Ils étaient repartés en plusieurs groupes, qui furent exposés respectivement aux causes suivantes de contamination.

Balayage et piétinement de la planche pendant, 4 minutes. C'était une planche de sapin, rabotée, de 100 x 31 cent.; 17 jours auparavant, 250 cc. de crachats bacillifères avaient été étalés sur toute la surface de la planche, en couche très mince. Le jour du balayage, la planche avait absorbé les crachats, et ceux-ci formaient, à la surface, des taches lisses d'apparence huileuse: il paraissait fort peu probable qu'un balayage de court durée pût reduire en poussière ces taches incluses dans le bois poreux.

Pendant 20 minutes, à plusieurs reprises, balayage et battage d'un tapis de moquette abondamment contaminé (Série 1). Ce tapis mésurait 153 x 63 cent. et avait été tendu sur un cadre de bois. Les 13^{e}, 12^{e}, et 11^{e} jours avant l'expérience, on avait étalé a la surface, a l'aide d'une spatule, quotidiennement, 125 cc. de crachats bacilliféres, tout en les mélangeant à de la poussière fine recueillie sur une armoire.

Le jour de l'expèrience, le tapis présentait nettement, à la surface, des trainers brillantes sèches et des petites écailles brillantes adhérentes.

Pendant 20 minutes, il a été, successivement, balayé avec un balai de sorgho, dressé verticalement et battu avec le manche du balai, puis balayé de nouveau, puis battu une dernière fois.

Pendant 12 minutes à plusieurs reprises, balayage et battage d'un tapis de moquette légèrement contaminé (Séries II). Ce tapis mésurait 50 x 110 cent. Le sixième jour avant l'expérience, on avait étalé a sa surface 20 cc. de crachats bacillifères.

Enfin un dernier groupe de cobayes (Série III) fut exposé successivement au balayage des deux tapis, et aux poussières soulevées pendant la période intercalaire (intervalle de 20 minutes).

Toutes les précautions furent prises pour écarter tout danger de contamination de l'opérateur, des assistants ou des locaux avoisinants; l'expérience a pu être faite sans précipitation, avec la sécurité et le calme nécessaires, grâce à l'appareil respiratoire du D^{r} Tissot, qui permet de séjourner pendant plusieurs heures dans une atmosphère irrespirable (gaz délétères, poussières infectieuses), tout en exécutant sans aucune gêne un travail musculaire intensif; l'expérimentateur, muni de cet appareil de sauvetage, était recouvert d'une cagoule protectrice avec vitre de mica. Un sas à air avait été installé au niveau de la fenêtre pour introduire les cobayes dans la chambre, ou les sortir, sans faire communiquer directement la chambre avec

Fig. 1.—Sas à air pour introduire les cobayes dans la chambre.

l'extérieur. Une lourde portière protégeait la porte; les fentes de la fenêtre étaient obturées par des bandes de papier. Enfin, après l'expérience, la chambre a été désinfectée d'une manière rigoureuse par des vapeurs de formacétone sous pression, suivant le procédé E. Fournier qui donne, comme nous nous en sommes assurés, une sécurité complète, même avec des crachats desséchés, difficilement désinfectables.

L'expérience a comporté plusieurs phases, et utilisé successivement plusieurs groupes de cobayes: les figures 2, 3, 4, représentent exactement, à l'échelle $\frac{1}{30}$, les places respectives occupées par ces cobayes.

Cette expérience a été instituée, non pas pour réproduire exactement les conditions de la contagion naturelle, mais pour étudier le mode de production des poussières tuberculeuses, lorsque des crachats de phtisiques, lentement déssechés dans les conditions mêmes de la dessiccation spontanée, sont soumis pendant peu de temps aux actions traumatisantes que se produisent dans la vie ordinaire. Mais, dans la vie ordinaire, ces action traumatisantes s'exercent d'une maniére bien plus efficace, grace a leur répétition incessante et à leur variété.

Nous sommes donc amenés aux conclusions suivantes:

1. Quand un tapis est contaminé par des crachats tuberculeux desséchés restés virulents, un seul balayage de quelques minutes, suivi de battage, suffit pour donner naissance à des poussières virulentes très fines, susceptibles de pénétrer dans les voies respiratoires profondes du cobaye et de créer une tuberculose d'inhalation.

2. La quantité de ces fines poussières libérée par un seul balayage est très minime par rapport à la quantité totale des crachats.

3. Ces poussières sont projetées par le balayage et le batage à une distance peu considérable des tapis, mais elles sont suffisamment fines et légères pour rester en suspension dans l'air pendant dix à quinze minutes, et pendant ce temps elles peuvent être transportées à distance par les mouvements atmosphériques.

Résultats.—Les deux cobayes exposés au déploiement du *mouchoir* (dessiccation de 25 jours) sont restés indemnes; ce résultat négatif est, sans doute, attribuable à la longue durée de la dessiccation; nous verrons, plus loin, qu'au 25^{e} jour la virulence des crachats desséchés à l'obscurité est notablement diminuée.

Les six cobayes exposés au balayage de la *planche* (dessiccation de dix-sept jours) sont restés eux aussi indemnes de tuberculose; il y a eu cependant, au cours du balayage, projection dans l'air de particules bacillifères à plus de 140 centimètres de hauteur, car les vingt litres d'air aspirés ont laissé sur le filtre des poussières virulentes; le cobaye inoculé sous la peau avec ces poussières, et tué au bout de deux mois, avait des lésions tuberculeuses en voie de généralisation viscérale; il est probable que le balayage

n'a pas mis en liberté des poussières suffisamment fines pour tuberculiser des cobayes par inhalation.

Les neuf cobayes exposés au balayage et au battage du *premier tapis* (*abondamment contaminé depuis onze à treize jours*), ont réagi d'une manière très démontrative (Fig. 3).

Quatre d'entre eux, exposés aux poussières à une petite distance du tapis, ont contracté des tuberculoses d'inhalation à évolution grave, entraînant la mort en deux à quatre mois. Les cinq autres, placés à d'assez grandes distances du tapis, sont demeurés indemnes. Il y a donc eu production de fines poussières bacillifères, mais ces poussières n'ont été pro-

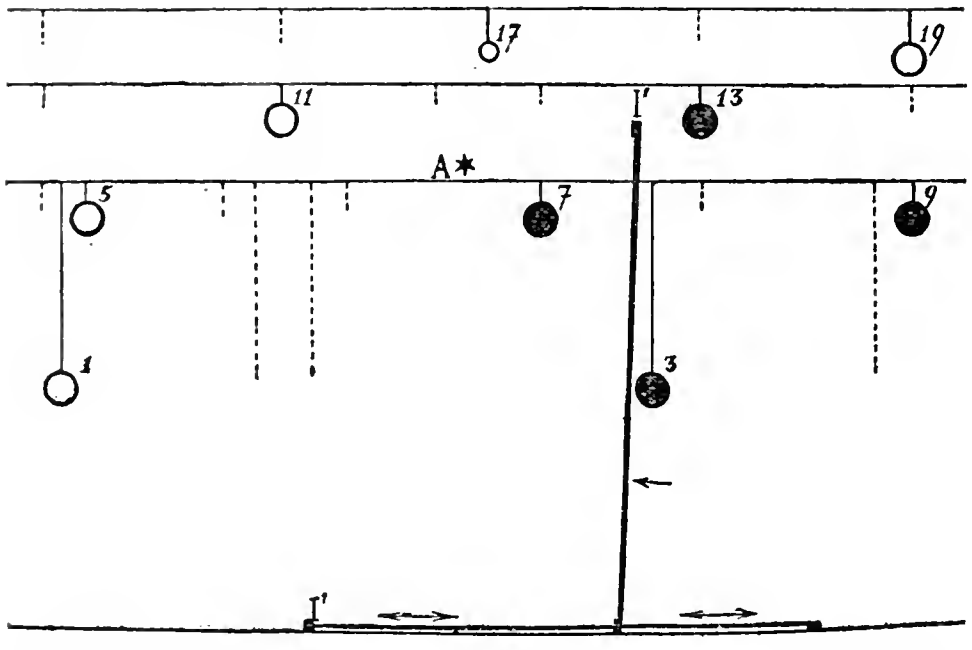


Fig. 3 (Echelle 1–30).—Balayage du premier tapis fortement contaminé.

Les cercles noirs figurent les cobayes morts de tuberculose; les cercles blancs figurent les cobayes restés indemnes. — En A, aspiration de 65 litres d'air au travers d'un filtre imperméable aux poussières. — I', première position du tapis, balayé sur le sol; II" deuxième position du tapis dressé verticalement pour le battage.

jetées par le balayage et par le battage du tapis qu'à une petite hauteur au-dessus de celui-ci. Le cobaye inoculé sous la peau avec les poussières des 65 litres d'air aspirés en A, est mort de tuberculose miliaire généralisée en cent jours.

Les six cobayes exposés au balayage et au battage du *deuxième tapis* (*discrètement contaminè depuis six jours*) n'ont été tuberculisés que dans une faible proportion (fig. 4).

Deux cobayes seulement ont présenté des tuberculoses à grave évolution; les quatre autres ont échappé à la contagion, bien qu'ils fussent placés à faible distance du tapis. Les poussières des 71 litres aspirés en A ont donné,

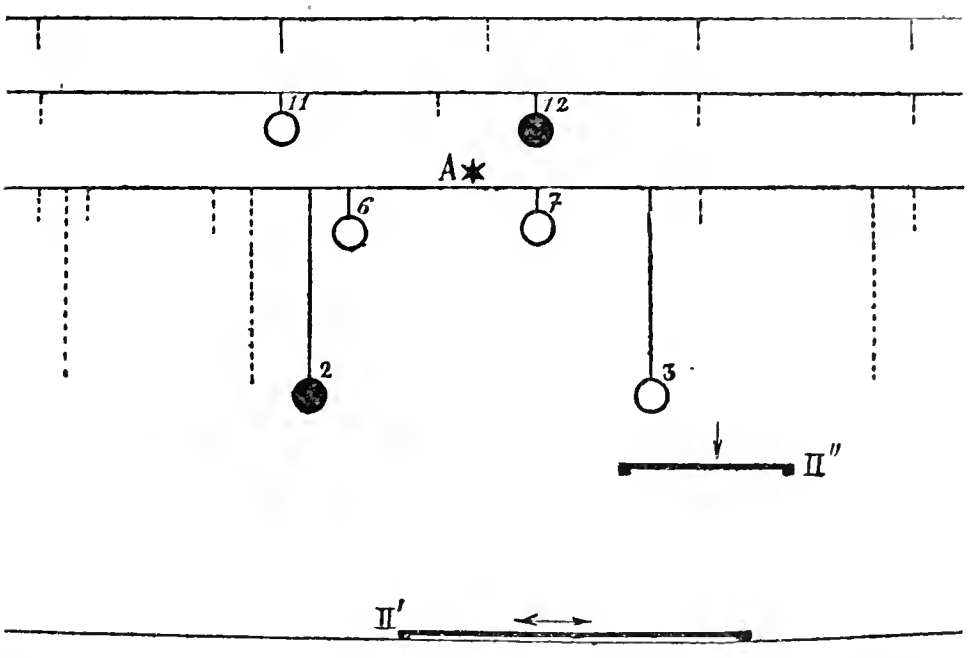


Fig. 4 (Echelle 1–30).—Balayage du deuxième tapis faiblement contaminé.

II′, première position du tapis, balayé sur le sol. — II″, deuxième position du tapis, posé horizontalement sur les genoux de l'expérimentateur assis, pour le battage. — En A, aspiration de 71 litres au travers d'un filtre aérien.

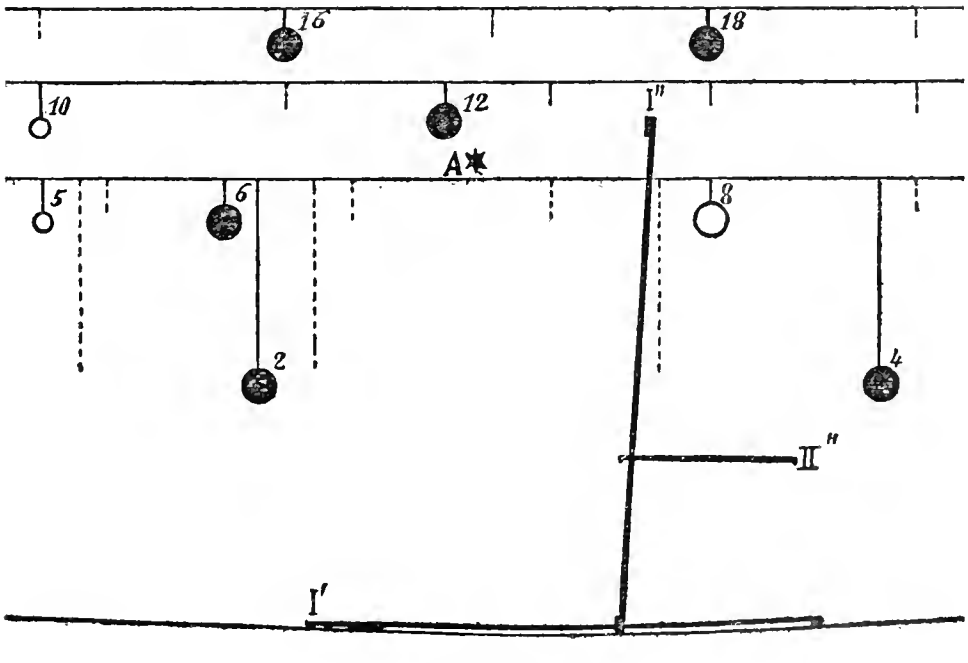


Fig. 5 (Echelle 1–30).

Cobayes exposés: 1° aux balayages du premier et du deuxième tapis; 2° aux poussières disseminées dans l'air par les mouvements incessants de l'operateur revêtu de la cagoule, pendant les vingt minutes d'intervalle entre les balayges des deux tapis.

par inoculation sous-cutanée au cobaye, une tuberculose miliaire généralisée, entraînant la mort en cent jours. En somme, ce tapis, faiblement contaminé et depuis peu, balayé et battu depuis peu de temps, a donné naissance à très peu de fines poussières bacillifères mobilisables.

Enfin, les neuf cobayes exposés au *balayage et au battage des deux tapis* sont devenus pour la plupart tuberculeux (Fig. 5); trois seulement ont échappé à l'infection, l'un d'eux (n° 8) sans motif apparent, les deux autres (n° 5 et n° 10), en raison de leur grand éloignement des tapis et de leur très jeune âge (cobayes de 125 grammes, ayant un courant inspiratoire très faible et des voies respiratoires très étroites). La prédominance des contaminations des cobayes de ce groupe ne s'explique guère par une simple superposition des influences auxquelles ont été soumis les cobayes des deux groupes précédents; une action *supplémentaire* a dû s'exercer, et cette action est représentée très vraisemblablement par les remous aériens et les mouvements atmosphériques provoqués dans l'intervalle de vingt minutes qui a séparé les balayages des deux tapis; la sortie des cobayes représentés Fig. 3, l'entrée des cobayes représentés Fig. 4, le placement de ces animaux aux endroits qui leur étaient assignés ont nécessité de nombreux mouvements de l'expérimentateur revêtu de sa cagoule: l'air de la chambre a été ainsi brassé dans une certaine mesure, d'ou dissémination plus grande des poussières produites par le premier balayage. D'ailleurs la cagoule ne pouvait, par elle-même, transporter des poussières mobiles, car elle était enduite de cire formant un revêtement gluant.

La mobilisation des poussières de balayage par les remous atmosphériques suppose comme première condition la *possibilité pour ces poussières de rester en suspension quelque temps dans l'air.* Aussi avons-nous entrepris des expériences pour étudier ce point particulier.

5. Les poussières virulentes produites et soulevées par le balayage d'un tapis contaminé restent elles en suspension dans l'air après la fin du balayage?

Mes expériences ont consisté à produire, dans la caisse d'inhalation, une poussière de balayage (avec des brosses de chiendent), exactement comme dans les expériences 4A, mais en n'introduisant les cobayes dans la caisse que 8 ou 10 minutes après la fin du balayage.

A ce moment, toutes les poussières un peu grossières s'étaient déposer au fond de la caisse: il ne restait en suspension dans l'air que de fines granulations poussiéreuses.

Or, ces expériences ont donné des résultats positifs: les cobayes exposés a des inhalations entrecoupées des poussières restées en suspension dans l'air, ont contracté des tuberculoses d'inhalation graves a évolution rapide, entrainant la mort en 50 a 70 jours.

6. Mecanisme pathogénique et aspect anatomopathologique des tuber-

culoses contractées dans une atmosphére de poussières tuberculeuses desséchées.

A. Ces tuberculoses sont des tuberculoses d'inhalation pures; la déglutition de poussière ne joue aucun rôle dans leur pathogénie.

B. Leur rapidité d'évolution est subordonnée à la virulence et à la quantité des poussières inhalées. Ces Tuberculoses d'inhalation sont toujour plus graves que les tuberculoses qu'on obtient par inoculation sous cutanée des poussières contenues dans l'atmosphère contaminé, alors même que la dose inoculée est notablement supérieure a la dose inhalée.

C. L'aspect des lésions varie suivant l'intensité de l'infection: mais dans bien du cas, on obtient ainsi, par voie expérimentale des tuberculoses exactement superposables aux formes anatomiques habituelles de la Tuberculose infantile primitive. (Tuberculose miliaire broncho-pneumonique, à foyers multiples—Tuberculose ganglio-pulmonaire primitive avec granulie terminale—Nodules d'inhalation sous-pleureux avec adénopathie médiastine—Foyers primitifs cavernulaires—Adénopathie médiastine prédominante, avec lésions pulmonaires minimes, entrainant la mort par pneumonie de compression ganglionnaire—Tuberculose ganglionnaire primitive du médiastin.)

DISCUSSION.

Prof. A. Calmette (Lille, France): I do not wish the impression to prevail that I in any way deny the frequency of tubercular infection by way of the respiratory system, but that, in the usual daily life, the infection of the digestive organs is predominant. This has been my constant position, which I wish to maintain, *i. e.*, the predominating infection of the digestive tract in the chronic clinical forms of tuberculosis. Bartel and Weichselbaum have pointed out the so-called lymphoidal stage of the bacillar infection, the tubercle bacilli infecting the digestive tract passing in small number to the corresponding lymph-glands, where they are held for a considerable time, being, so to speak, encapsulated in the gland. Especially in cattle and other animals such glands are capable of infecting guinea-pigs even after three months of infection of the original animal. After this three months' time the glands are generally no longer infective when injected into guinea-pigs.

When the bacilli enter through the circulation, they likewise penetrate the lymph-glands, but here persist in the glands indefinitely. In the Behring revaccination such bacilli are held in these glands most persistently. There is no sign of their extinction. The intravenous injection of bacilli infects glands of cattle, which cattle maintain every appearance of good health long after that gland substance when injected into a guinea-pig

shows the infectibility. This appearance of good health may continue for a long time until a sudden breakdown of the gland permits a general infection of the creature, and the general phenomena of bacillary invasion result.

Infection of the respiratory tract is in many cases undeniable, as, for instance, a nursing child absorbing the tubercular infection from its mother's sneezing or coughing, but where the respiratory tract is healthy, its infection by tubercular germs would be rare, except in cases of exposure like those of the experiments of Dr. Kuss, which conditions of exposure are not those of normal surroundings. The infectious contagion of the tubercle bacilli by handshaking, flies, soiled food, is far more likely to infect by the ingestion of these bacilli through the mouth and the digestive tract than by any infection of the respiratory tract in the conditions of every-day life.

This repeated every-day reinfection with fresh tubercle bacilli is the dangerous infection of tuberculosis. It must be remembered that the function of the lymphatic gland is not an indefinite one in its duration, that a time comes when this functional arrest of the germs by the gland is overcome by the constantly recurring infections, and consequently the infection of the entire organism results and a chronic tuberculosis is initiated.

Where the respiratory tract is primarily infected, it is more usual to have the pneumonic—caseous—type of pulmonary infection.

Prof. Landouzy (Paris) said that, in reading this paper, he confined himself to representing its author; that he now wishes to speak for himself.

He indorses the ideas of Dr. Calmette, and last year quite widely proclaimed his position and conclusion, that it really requires quite special conditions to establish a primary infection of the respiratory tract. These special conditions may be an otherwise induced inflammation of the mucosa of some portion of the respiratory system—a catarrhal condition. The good sense of the ancients is well shown in their insistence upon a preëxisting catarrh to constitute an open door to tuberculous infection. The special rôle of measles in this connection was as well known to the ancients as to us. The typhoid inflammation and other catarrhs of infectious disease all hinder an active phagocytosis, and to this degree facilitate the establishment of tubercular infection.

It is a well-known fact that very few individuals that have undergone tracheotomy in their infancy ever reach an age superior to twenty years. It is statistically established by the military surgeons of France that a tracheotomized individual appearing for military service (twenty-one years old) is a very great rarity. German statistics have also completely established this point. An explanation of this precocious death of such individuals would be found in that the wound has created in its healing a zone of cicatricial tissue, totally devoid of any possibility of phagocytic reaction and consequent protection against invasion by the bacilli.

A large mass of statistics, relating to tuberculosis of the larynx, has demonstrated the frequent preëxistence of syphilis. The secondary accidents of this disease, commonly occurring in the larynx, provoking lesions the healing of which would produce localized cicatricial tissue, a consequent lack of phagocytosis, and easy local infection by the tubercular germ, the rapid development of which, at this point, is the tubercular laryngitis.

Dr. Mazÿck P. Ravenel (Madison, Wisconsin): Experiments in animals show the overwhelming frequency of alimentary infection. Tubercle bacilli administered in melted butter by stomach-tube show, for instance, that three hours after injection the tubercle bacilli could be recovered from the mesenteric glands. Injections of similarly prepared cultures of tubercle bacilli injected directly into the stomach after laparotomy led to the discovery of tubercle bacilli in the lungs within a few (three and a half) hours after the injection. Particular importance should be attached to the work of Rabinowitch, who, after occlusion of the esophagus and preparation of a gastric fistula, injected tubercle bacilli directly into the stomach and found tubercle bacilli in nearly all the organs within twenty-two to twenty-four hours. Aside from this purely experimental evidence, a number of observations made in cattle by the Wisconsin authorities possess almost the value of an experiment. It has been shown conclusively that the spread of tuberculosis among cattle follows very largely the distribution, for food purposes, of skim-milk and other creamery products.

In infected swine it will be found that the tuberculous process almost invariably, that is, in fully 90 per cent. of the cases, began in the retropharyngeal glands. No one has ever claimed that infection of swine occurs by the respiratory route, or that the disease is spread by secretions from the respiratory passages.

All this evidence in animals, of course, does not negative the occurrence of respiratory infections in human beings. One must take an impartial view of the whole problem, and be willing to agree that both channels of infection are open. In animals, however, the alimentary tract seems to be a more common port of entry.

CONCERNING LATENT TUBERCULOSIS.

By Professor Francis Harbitz,
Kristiania, Norway.

In our time the view is still commonly held that tuberculosis observable by clinical methods is, as a rule, a result of an infection that remains latent but a comparatively short time—from months up to a few years—before tuberculosis appears in the child or in the adult; and the regulations against tuberculosis, whether taken secretly or openly, have, to no small degree, their starting-point from this idea.

Recently, however, a doubt has arisen concerning the accuracy of this view, especially since it has been shown how extremely common tuberculosis is during the years of childhood. Indeed, some contend that the majority of cases of tuberculosis are due to infection in childhood or infancy, presupposing a very long period of latency. The German writer, Dolland, has drawn such inferences from a clinical point of view. Dr. L. F. Flick has also remarked that "tuberculous infection takes place in early life; some throw off the disease and become completely sterile, no doubt; but many carry the microörganisms through life, and either develop the disease in a fatal form, or maintain it in a dormant condition in the lymphatic system."

A Norwegian medical writer, Andword, has also repeatedly and emphatically expressed similar views in his articles on the subject. He argues from the extreme frequency of tuberculosis found by anatomical research in persons of all ages, even during the first years of childhood. He contends that fresh tubercles, in development, can be shown to exist in cases of sudden death or of death from acute illness, in 8 per cent. to 9 per cent. of the population. Thus, for instance, in a town of 210,000 inhabitants, 17,000 would be infected with tuberculosis, and it would have a tuberculous mortality of about 3½ per cent. of the whole living population; that is, about 750 deaths from tuberculosis per annum; and we should conclude from this that the average duration of these cases of tuberculosis would be about twenty years. He argues that, in the majority of deaths from tuberculosis among adults (Andword thinks about 80 per cent. of the whole), the period of infection must be referred back to childhood. At the same time, however, Andword believes that most of the cases of infection in childhood are cured and acquire immunity against subsequent infection.

The question as to the accuracy of these deductions is at present an open one, and as, during my researches on tuberculosis in children, I have touched on the latency of tuberculosis, and,—to come to the point at once, since I do not agree with the application, especially of the results of the different anatomical investigations,—I wish to accentuate my standpoint in this matter.

So far as adults are concerned, it is now generally conceded that it is possible to demonstrate tuberculosis, or the traces of it, in most people (about 40 to 50 to 60 per cent.), at any rate, among the people of the larger towns. In systematic investigations during the post-mortem examinations of 558 adults, which I carried out in Kristiania during the years 1901–1903, I found tuberculosis in about 70 per cent., while only about 22 per cent. of the deaths were from tuberculosis; latent and obsolete tuberculosis among about 42 per cent., increasing greatly in frequency with age; and fresh virulent tuberculosis (in development) in about 5 to 6 per cent., which corresponds with reports from other countries.

But tuberculous infection can also be demonstrated very frequently among children—far more frequently than is generally supposed. At 275 post-mortems of children I found tuberculous infection in 42 per cent.; in my last series, in which a systematic examination of the lymphatic glands with the microscope and inoculations was undertaken, as many as 48.5 per cent. (that is, nearly half). The number of infected cases increased rapidly with age, there being about 20 per cent. in the first year of life, 26 per cent. in the second, 40 per cent. in the third and fourth, and as many as 80 per cent. in the ages from five to fifteen. Similar results, although not quite so high, are found in other countries. Here in America Hand found about 34.5 per cent.; Councilman, Mallory, and Pierce found, among children who had died from diphtheria, 16 per cent. of tuberculous cases, which is considerably less. According to a larger work from Vienna, published recently by Hamburger, tuberculosis was found in 40 per cent. of the cases examined, in about 17 per cent. of whom it was a chance discovery.

So far as concerns my own experiences of tuberculous infection among children (in all, 117 cases were investigated), I found that about 60 per cent. had died of tuberculosis, while a latent (or, rarely, obsolete) tuberculosis was found in 16.5 per cent.; or, if the mortality from tuberculosis be deducted therefrom, about 22 per cent., or one-fifth of the total number. Among the latent infections occasionally discovered, I may mention the occurrence in lymph-nodes of tubercle bacilli, demonstrable by inoculation, apparently without concurrent macroscopical or microscopical changes. This has since been confirmed by similar researches carried out by Weichselbaum and Bartel, Rosenberger, Weber, Baginsky, Gaffky (who found tuberculosis in 11 per cent. of 300 children aged up to thirteen years, and latent tubercle bacilli

among 11 per cent. of the remaining cases), Goodale, J. H. Wright and Smith, and others. The correctness of the assumption that tubercle bacilli may be present in relatively healthy lymphatic glands has been contested by Joest, who always has a microscopical tuberculosis demonstrated, and so desires to attribute these cases, also, to latent tuberculosis. Be this as it may, these cases, at any rate, increase the number of latent infections in childhood to a marked extent.

But what is the significance of this latent tuberculosis in children? Many cases of latent tuberculosis in children, just as in adults, are cured. This must be kept in mind, and a conclusion drawn from a regular development of all these cases is scarcely justified. On the other hand, we see that a great many cases of tuberculosis, especially of the lymphatic glands of children, remain for a long time, from year to year, either in a single lymphatic gland group, or, by degrees, entering one group after another, so that infection during childhood simply continues in the adult. Many proofs of this can be produced. It is, for instance, an ordinary clinical experience, such as hospitals for scrofulous children give excellent opportunities for, that a great number of scrofulous children are not cured—or, at least, only temporarily cured—but die as adults, most frequently in youth, of tuberculosis that must, as a rule, be referred to infection in childhood.

Moreover, we often see instances of this at autopsy, when once we begin to search for them. Adults not infrequently die of tuberculosis, generally affecting the lymphatic glands or the inner organs; and, partly by the aid of information obtained from records of the history of illness, and partly from the presence of tuberculosis in the lymphatic glands, we are led to the conclusion that there has been tuberculous infection for a long period, in fact, from childhood, and, to a large extent, latent. In a series of cases I have been able to establish the presence of such a latency for ten, twenty, thirty years. However, these cases are—even when attention is specially directed to them during the post-mortem examinations—in the minority among all the deaths from tuberculosis in adults. Thus, in the material investigated by me only about 20 per cent. of the whole number of post-mortems exhibited such chronic latent tuberculosis; and among stray instances of mortality from tuberculosis, even fewer (about 10 per cent.), but not the majority of cases of tuberculosis in adults, as is claimed by some authors.

Although, so far as anatomy is concerned, definite evidence is lacking, as to tuberculosis carried on from childhood, we might, nevertheless, think that infection with tubercle bacilli could remain and become significant, because, *per se*, there is nothing against the idea that tubercle bacilli may remain almost unchanged for a considerable period (for instance, in the lymphatic glands), though living and virulent. There are analogous cases

to be found with other microbes; for instance, the leprosy bacilli, which are known to live for years, even decades, stored up (*e. g.*, in the ganglion-cells in the nervous system), without either bacilli or cells showing perceptible changes. Yet we are not at present able to produce any proof that tubercle bacilli behave in the same way.

It is another matter that a latent infection in childhood, of whatever nature it may be in other ways, may certainly produce an effect in the organism, even though the result may not be a tuberculous inflammation. Infection received in childhood could thus be assumed, on the one hand, to produce a predisposition to a new infection taken in adult years, and, on the other hand, to give immunity against new infection.

In the former case a new infection—a reinfection—must take place. At post-mortems we not infrequently meet cases where we find traces of an older tuberculous infection which has been cured, and, at the same time, fresh tubercles having no connection with these. Repeated infections, with considerable intervals between, must have taken place; but, whether it happens that the first infection has produced an augmented disposition is a difficult matter to decide. Anatomical evidence of this has not been procured, and experimental proofs have not been brought to my notice. But there is much to support the opinion that a tuberculous infection, from which recovery has been made, leaves its traces, occasions a certain debility, and creates a predisposition to tuberculosis, as well as to other diseases. It is, at any rate, certain that tuberculosis of the lymphatic glands, recognized by clinical methods, after apparent recovery, is no triviality, but often gives rise to a fatal galloping consumption in adults, whether it is to be considered as a directly continued infection, or only as a predisposition to new infection.

So far as concerns the supposed immunity, which a thorough tuberculous infection in childhood might produce, it is, for the time being, a hypothesis. Of itself, it is not very probable that a little tuberculous inflammation (*e. g.*, in a lymphatic gland) should produce immunity throughout a long life; still less probable is it, so far as concerns a case of the so-called "latent tubercle bacilli," which certainly soon get absorbed and vanish. Neither must we leave out of consideration the not infrequent cases in which traces of repeated tuberculous infection ("reinfection") are discovered, because such cases certainly argue against immunity after infection. Neither can experimental work be considered in support of such assumptions.

Conclusions.—At present, anatomical proofs are lacking to show that the majority of cases of tuberculosis in adults are due to infection during childhood, with a long period of latency and continued slow tuberculous inflammation.

However, considering the frequency of tuberculosis among children, and

the evidence of its slow development through years and even decades, infection during childhood must certainly be considered of great significance.

Proofs are, at present, not forthcoming as to whether tuberculous infection in childhood, with a subsequent complete restoration to health, produces an increased predisposition to new infection; but neither have we, on the other hand, any proofs to the contrary.

DIE DISPOSITION DER LUNGENSPITZEN ZUR TUBERKULÖSEN PHTHISE.

(DAS LOKALISATIONSGESETZ DES INITIALEN TUBERKULÖSEN LUNGENHERDES.)

By Dr. Carl Hart,
Berlin.

Der Kampf gegen die mörderische Volkskrankheit, welcher hier so viele hervorragende Männer fast aus aller Herren Länder zu gemeinsamer Beratung geeigneter Massnahmen zusammengeführt hat, muss ein sehr umfassender sein. Es gilt nicht allein, den Tuberkelbazillus an der Verbreitung und Vermehrung, an der Invasion immer neuer Menschen zu hindern, sondern unser Augenmerk hat sich auch speziell in Hinsicht auf die Tuberkulose nach den allgemein gültigen Gesetzen einer wirksamen Hygiene darauf zu richten, kräftige, gesunde und widerstandsfähige Menschen heranzuziehen. Denn wir dürfen nicht vergessen, dass der Ausbruch einer progredienten tuberkulösen Lungenphthise, welche ja die häufigste und für die Verbreitung des tuberkulösen Virus gefährlichste Form der tuberkulösen Erkrankung des Menschen darstellt, nicht allein von der Infektion, sondern auch von der individuellen Disposition abhängig ist. Die uralte Streitfrage über die Bedeutung der Disposition dürfte ja jetzt, nachdem wir gelernt haben, an Stelle der alten vagen und mystischen Begriffe sehr reale anatomische, chemische, funktionelle, überhaupt biologische Tatsachen zu setzen, im allgemeinen gelöst sein, aber viel, sehr viel Einzelarbeit wird noch nötig sein, wollen wir in exakt wissenschaftlicher Weise die Mannigfaltigkeit der tuberkulösen Erkrankung—soweit die stets variable Disposition des Individuums in Betracht kommt—verstehen und erklären lernen.

Das Studium aller Momente, welche als disponierende zu betrachten und in Gemeinschaft mit der Invasion des Tuberkelbazillus als Ursache der tuberkulösen Lungenphthise zu bezeichnen sind, kann kein müssiges sein. Denn, um an ein Wort Birch-Hirschfelds zu erinnern, "jeder Fortschritt in der Erkenntnis der Faktoren, die das Zustandekommen und den Verlauf der tuberkulösen Lungenschwindsucht wesentlich beeinflussen, muss für die Bekämpfung der verbreiteten Volkskrankheit Gewinn bringen, weil dadurch die kritische Feststellung der Wirksamkeit von Schutz- und Angriffsmitteln

gegen Verbreitung, Festsetzung und Fortentwickelung der tuberkulösen Infektion erleichtert wird."

Die tuberkulöse Lungenphthise zeigt in ihren initialen Stadien eine derart charakteristische Lokalisation, von diesem Typ abweichende Lokalisationsformen sind so auffallend, endlich ist der Unterschied in erster Lokalisation und in Form der tuberkulösen Lungenerkrankung bei Kindern und Erwachsenen ein so bemerkenswerter, dass es nahe genug liegt, um ein kurzes Wort zu gebrauchen, das Lokalisationsgesetz des ersten tuberkulösen Erkrankungsherdes der Lungen zu studieren. Die Hoffnung, dass sich aus solchen Forschungen sichere Schlüsse bezüglich der Bedeutung einer individuellen Disposition ergeben werden, wird sich am Schlusse dieser Ausführungen, wie ich hoffe, in schönster Weise erfüllt zeigen.

Da durch eine ganze Anzahl sorgfältigster Untersuchungen festgestellt worden ist, dass die Mehrzahl der Menschen vor allem in den grossen Städten und Industriezentren tuberkulös infiziert wird, aber nur ein relativ kleiner Prozentsatz an einer progredienten Lungenphthise erkrankt und stirbt, so erscheint die Annahme einer individuellen Disposition, will man nicht in der Wirkung des Tuberkelbazillus allein die Erklärung suchen, geradezu als ein Postulat. Betrachtungen und Untersuchungen über die respiratorische Tätigkeit der Lungenspitzen allein, ihre Blut- und Lymphversorgung, den Bau ihrer Bronchien führen aber nicht zum Ziele, denn es ergeben sich nur allgemeine, für alle Menschen in gleicher Weise zutreffende Verhältnisse, welche das individuell so ausgesprochen variable Verhalten gegenüber der tuberkulösen Infektion nicht erklären.

Nur eine Lehre, welche vor nunmehr zwei Menschenaltern W. A. Freund mit wahrhaft genialem Blick begründete, wird dem Lokalisationsgesetz der tuberkulösen Lungenphthise gerecht und hat sich für einen weiteren Ausbau als überaus fruchtbar erwiesen. Auf dem Boden der noch heute gültigen Feststellungen F r e u n d s stehend, konnte ich eine präcise Lehre von der mechanischen Disposition der Lungenspitzen zur tuberkulösen Phthise aufstellen und neuerdings in Gemeinschaft mit H a r r a s s den Versuch machen, das schwierige und vielumstrittene Problem des Thorax phthisikus zu lösen. Das Fundament aller neueren Untersuchungen ist die Freund'sche Lehre von der Stenose der oberen Thoraxapertur. Diese besagt etwa folgendes. Bei einer grossen Anzahl jugendlicher, meist hereditär belasteter Phthisiker findet sich eine einseitige oder doppelseitige abnorme Kürze der ersten Rippenknorpel. Sie beruht, da sich ihre ersten Anfänge bis in das früheste Kindesalter hinein zurückverfolgen lassen, auf einer infantilistischen Entwickelungshemmung, die entweder das Knorpelwachstum dauernd hemmt oder zu einem vorzeitigen Stillstand bringt. Infolge der abnormen Kürze der ersten Rippenknorpel kommt es zu einer allgemeinen Beengung des kartenherzförmigen Aperturringes und des weiteren durch den unausgesetzt

wirkenden Reiz der mit grosser Kraft, weil schwer auszuführenden inspiratorischen Torsion des verkürzten Knorpels zu einer ossifizierenden Perichondritis, einer scheidenförmigen Verknöcherung, welche schliesslich zur völligen Unbeweglichkeit des Knorpels und damit zur totalen Funktionsuntüchtigkeit der oberen Thoraxapertur führt. Denn da der erste Rippenknorpel fest und ungelenkig mit dem Manubrium sterni verbunden ist, kann die einzige für die obersten Rippen mögliche Bewegung, die durch die Axe des Rippenhalses vorgeschriebene respiratorische Hebung und Senkung allein mit einer inspiratorischen Spiraldrehung des Knorpels von statten gehen, deren Spannung dann auch der Exspiration zugute kommt. Bei der durch abnorme Knorpelkürze bedingten Stenose der oberen Thoraxapertur muss also das Gewebe der vom ersten Rippenring umschlossenen Lungenspitzen in doppelter Weise geschädigt werden, einmal durch den Druck des verengten Rippenringes und zweitens durch die Funktionshemmung, welche sich ja ganz gesetzmässig aus der Erstarrung der Apertur ergeben muss.

Die genauere Analyse diesser Schädigungen haben erst Untersuchungen der letzten Jahre gebracht, welche zunächst im wesentlichen die Freund'schen Angaben bestätigten, dann sie aber auch erweiterten und dem Verständnis näherbrachten. Freund selbst ist noch ein eifriger Arbeiter am Ausbau seiner Lehre. Meine eigenen, seit Jahren an mehreren hundert Phthisikerleichen wie auch an lebenden phthisisch veranlagten, nicht erkrankten Personen vorgenommenen Untersuchungen haben zunächst festgestellt, dass neben der abnormen Kürze der ersten Rippenknorpel entweder isoliert oder mit dieser kombiniert eine rudimentäre Entwickelung der ersten Rippe selbst vorkommt, die sicher eine primäre, angeborene Anomalie darstellt. Die Apertur muss natürlich infolge dieser Anomalieen mehr oder weniger stenosiert werden. Allein diese Stenosierung der oberen Thoraxapertur ist für gewöhnlich keine allgemeine, sondern—sei es nun, dass die Rippe direkt verbildet ist, sei es, dass gewisse Anpassungsbestrebungen zu einer Streckung ihrer Form führen—es kommt zu einer Formveränderung der Apertur, die aus der querovalen in eine mehr gradovale, in jeder Hinsicht an die phylogenetisch tiefstehende primäre Aperturform der Säugetiere erinnernde übergeht. Das bedeutet nichts anderes, als dass infolge einer Streckung der Rippe, welche ihr einen steil nach vorn gerichteten Verlauf gibt, die seitlich hinteren paravertebralen Ausbuchtungen der Apertur, in denen die Lungenspitzen sich entfalten und bewegen, eine räumliche Beengung erfahren. Diese Beengung und Abänderung der oberen Thoraxapertur wird deshalb des weiteren noch bedeutungsvoll für das umschlossene Lungenspitzengewebe, als die stenosierte Apertur, wie schon Freund festgestellt hat, eine gegen die Norm grössere Neigung zur horizontalen einnimmt und damit die Spitzenkegel der Lungen an einer tieferen und daher grösseren

Circumferenz umfasst. Dazu kommt in der Tat schliesslich infolge einer früh sich entwickelnden scheidenförmigen Verknöcherung der Rippenknorpel eine Erschwerung der respiratorischen Funktion der Apertur, die in extremen Fällen zur völligen Unbeweglichkeit führen kann.

Alle diese Beobachtungen haben inzwischen zahlreiche Bestätigungen gefunden und der Beweis, dass es sich bei diesen Aperturanomalieen nicht etwa um Folgen der tuberkulösen Spitzenphthise, sondern um primär gegebene, der Lungenerkrankung vorausgehende Grundübel handelt, darf als ein bis ins Einzelne geführter betrachtet werden.

Sind nun diese Anomalieen der oberen Thoraxapertur die Ursache der Spitzenerkrankung, soweit der dispositionelle Faktor in Betracht kommt? Das ist wohl mit Sicherheit zu behaupten.

Es ist zunächst ohne weiteres verständlich, dass—eine zur Körperlänge im proportionalen Verhältnis stehende mittlere Aperturweite vorausgesetzt—eine Stenose des ersten Rippenringes zu einer Beengung der Pleurakuppel und damit einer Behinderung der Lungenspitzenentfaltung führen muss. Die zuerst von Freund beobachtete, von mir und anderen bestätigte, keineswegs übermässig seltene gleichzeitige Verkürzung der zweiten Rippenknorpel, meist die Teilerscheinung eines allgemein verengten Thorax, trägt zur Beengung der Pleurakuppel ihrerseits bei. Die Entwickelung der Lungenspitzen, welche wir uns als eine vorerst gesunde, dem allgemeinen Wachstum kongruente vorstellen dürfen, muss zur Zeit, wo die anatomischen Schädigungen am ersten Rippenringe mehr oder weniger plötzlich manifest werden, sich einem absoluten Missverhältnis zwischen der ihr innewohnenden Entfaltungstendenz und dem gegebenen Raume gegenüber stehen. Aber die Beengung der Lungenspitzen bei Stenose der oberen Thoraxapertur findet in der scharf umschriebenen Einschnürung durch den ersten Rippenring noch ihren besonderen Ausdruck. Das sinnenfällige Merkmal ist die von Schmorl entdeckte subapikale Lungenfurche, die sich entsprechend der von mir erkannten Streckung der ersten Rippe und räumlichen Beeinträchtigung der seitlich-hinteren Aperturausbuchtungen an der hinteren und seitlichen Fläche des Lungenspitzenkegels zeigt. Und dieser Druckfurche entsprechend finden wir als wertvolles gleichwertiges Zeichen der Kompression des Lungenspitzengewebes im Innern die von Birch-Hirschfeld zuerst beschriebene und späterhin vielfältig bestätigte Zusammendrängung, Abknickung, Verkrümmung und Stenosierung der hinteren subapikalen Spitzenbronchien.

Es ist bezeichnend, dass neben anderen gerade diese beiden Forscher die erste Lokalisation des tuberkulösen Erkrankungsherdes im Bereich der Druckfurche und der Abknickung der Bronchialäste als primäre Tuberkulose der Bronchialschleimhaut resp. der Bronchialwand fanden. So kurz ich mich auch fassen muss, will ich doch diese Befunde, welche auf

sorgfältigster Durchmusterung eines grossen Sektionsmaterials beruhen, genetisch erklären. Die mangelhafte Entfaltungsmöglichkeit der Lungenspitzen bedeutet bereits an sich eine Einbusse respiratorischer Kraft, weil das Gewebe anscheinend in halbkollabiertem Ruhezustand verharrt. Darauf weist der röntgenographische Befund von Schatten über den Lungenspitzen bei paralytischem Thorax hin, welche bei längeren systematischen Atemübungen schwinden. Denken wir nun daran, dass der abnorm kurze Knorpel rigider als der normal entwickelte ist, dass die damit gegebene Erschwerung der respiratorischen Bewegung des obersten Rippenringes durch die frühzeitig einsetzenden Verknöcherungsprozesse weiterhin selbst bis zur völligen Bewegungsunmöglichkeit gesteigert werden kann, dass aber bei Individuen mit derartigen Aperturanomalieen ganz unbewusst sich eine dauernde Verflachung der Atmung an der oberen Thoraxpartie einstellt, so vermögen wir zu ermessen, wie deletär die Apertursstenose wirken muss. Es wird sich nicht nur nie eine ausgiebige Entfaltung der Lungenspitzen auch nur vorübergehend ermöglichen, sondern entsprechend den Untersuchungen Birch-Hirschfelds wird auch in den Spitzenbronchien eine "tote Rohrstrecke" entstehen, in welcher die Luft sozusagen stagniert, wo aspirierte Staubteilchen und Bazillen leicht liegen bleiben und zu Katarrhen der Schleimhaut Veranlassung geben. Die Abknickung und Stenosierung des Bronchiallumens muss ganz notgedrungen dazu beitragen, dass die katarrhalischen Sekretmassen liegen bleiben und so den besten Nährboden für Tuberkelbazillen darbieten, welche schliesslich die Bronchialwand selbst infizieren. Ja, man möchte fast glauben, dass die Umschnürung des Lungenspitzenkegels durch den starren funktionsunfähigen ersten Rippenring die Aspiration infektiösen Materials direkt begünstigt, indem sie gleichsam zwei Lungenbezirke von verschiedener respiratorischer, ganz besonders exspiratorischer Kraft gegen einander abgrenzt. Es kann so leicht das eintreten, was Orth ohnehin nicht für ausgeschlossen hält: bei kräftiger Exspiration der unteren Lungenabschnitte wird die minderwertige Exspirationsluft in die still-liegenden Spitzenbezirke gedrückt, in welchen sie still steht und wo sich die in ihr enthaltenen korpuskulären Elemente bequem absetzen können. Die Erfahrungen, welche ich über Spitzenanthrakose bei Stenose der oberen Thoraxapertur sammeln konnte, scheinen deutlich für einen solchen Vorgang zu sprechen.

Ohne dass ich diese interessanten Ventilationsvorgänge eingehender besprechen kann, muss aber nun auf die weitere Tatsache eminentester Bedeutung hingewiesen werden, dass auch die Blut- und Lymphcirculation bei Stenose der oberen Thoraxapertur im Bereich der Lungenspitzen schwer leiden. Denn aus bekannten physikalischen Gesetzen ergibt sich, dass Blut- und Lymphcirculation in den Lungen von der Ventilation in hohem Masse abhängig sind, ganz abgesehen davon, dass die Umschnürung des

Spitzengewebes direkt zur Kompression der dünnwandigen Gefässe führen wird.

So ergibt sich denn die Berechtigung zu folgenden, von mir aufgestellten Sätzen: "Die Stenose und Funktionshemmung der oberen Thoraxapertur schafft in den Lungenspitzen eine individuelle Disposition für die aërogene, hämatogene und lymphogene tuberkulöse Infektion. Es ist nicht nur eine günstige physikalische Gelegenheit zur Ansiedlung der Tuberkelbazillen gegeben, sondern mit der Schädigung des Gewebes entsteht ein günstiger Nährboden, in welchem die Bazillen sich vermehren und ihre verheerende Wirkung entfalten können.

"Der Endausgang des Existenzkampfes zwischen Tuberkelbazillen und Gewebszellen ist in allen Fällen, mag es sich um eine aërogene, hämatogene oder lymphogene Infektion handeln, abhängig von der Schädigung des Lungenspitzengewebes. Da nun die Blutcirculation, durch welche das Gewebe ernährt wird, sowohl direkt durch den auf dem Gewebe lastenden Druck als auch indirekt durch die Beeinträchtigung der Ventilation bei einer Stenose und Funktionsstörung der Apertur geschädigt ist, bleibt in letzter Hinsicht die Widerstandskraft des Gewebes und der Endausgang des Kampfes abhängig von den mechanischen Verhältnissen der oberen Thoraxapertur."

Bevor wir nun diese Sätze auf Grund der klinischen und pathologisch-anatomischen Erscheinungsformen der menschlichen Lungentuberkulose auf ihren Wert prüfen, wollen wir noch die Genese der Aperturanomalieen näher ins Auge fassen. Sie ist, wie ich gemeinsam mit Harrass feststellen konnte, eine mehrfache, und es erscheint bedeutsam genug, von vornherein primäre angeborene und sekundäre während des Lebens erst erworbene Aperturanomalieen, welche im wesentlichen einer Stenosierung gleichkommen, zu trennen. Zunächst besteht nach wie vor für viele Fälle die alte Freund'sche Auffassung zu Recht, dass es sich um infantilistische Hemmungsbildungen handelt, welche das Stehenbleiben der Apertur auf einer frühen Entwickelungsstufe meist in Gestalt der phyletisch tiefer stehenden, längsovalen Aperturform erklären. Es ist die geringe Entwickelungskraft an ersten Rippen und Rippenknorpeln nicht nur mehrfach bis in das früheste Kindesalter hinein zurückverfolgt worden, sondern es weist auch die häufige Koinzidenz mit anderen in gleichem Sinne zu deutenden Organzuständen, von denen vielleicht die Hypoplasie des Herzens und arteriellen Gefässsystems am wichtigsten ist, deutlich darauf hin, dass die Aperturstenose vielfach nichts anderes ist als der Ausdruck einer minderwertigen Allgemeinkonstitution, welche dem Individuum eine geringe Widerstandskraft im Kampfe des Daseins verleiht. Diese Entwickelungsanomalieen sind den Gesetzen der Vererbung unterworfen, obwohl wir in letzter Hinsicht noch nicht klar die Relationen zwischen Keimzelle und obere Thoraxapertur

zu erkennen vermögen und ausser Stande sind, anzugeben, ob primäre Keim- oder Somavariation vorliegt. Ich möchte aber hervorheben, dass aller Wahrscheinlichkeit nach diese Heredität keine streng spezifische ist in dem Sinne, dass sie allein auf tuberkulöser Verseuchung der Ascendenz beruht, sondern dass überhaupt jede schwere Schädigung der Keimsubstanzen, wie sie neben der allerdings in erster Linie stehenden Tuberkulose weiterhin auch Syphilis, chronischer Alkoholismus und andere Noxen hervorrufen können, entwickelungshemmend auf die Nachkommenschaft wirken. Dass bei sorgfältigen Untersuchungen aus dem Bilde des psychisch-physischen Infantilismus sich gewisse Anomalieen der oberen Thoraxapertur so bedeutsam herausheben, ist vielleicht darauf zurückzuführen, dass gerade die jetzige Gestalt der oberen Apertur eine junge phyletische Acquisition als Folge des aufrechten Ganges und freien Gebrauches der Arme ist, welche noch keineswegs ein absolut fester Besitzstand des artfesten Menschen geworden zu sein scheint.

Nun müssen wir uns nur noch einer überaus wichtigen Tatsache bewusst bleiben. Die abnorme Kürze der ersten Rippen und ihrer Knorpel ist nicht in strengem Sinne eine angeborene, sondern angeboren ist nur die Konstitutionseigentümlichkeit, die Krankheitsanlage, die nicht schon zur Zeit der Geburt notgedrungen vorhanden sein muss, vielmehr fast ausschliesslich erst im Laufe der Entwickelung, namentlich zur Zeit der Reife in Erscheinung tritt und durch das Missverhältnis der anatomischen Korrelationen ihre deletäre Bedeutung erlangt. Die Bedeutung dieser sicheren Feststellung wird sogleich erhellen.

Wie nun meine neuen mit Harrass ausgeführten umfangreichen Untersuchungen, welche darauf gerichtet waren, eine präcise Definition des echten Thorax phthisikus zu schaffen, ergeben haben, gibt es neben den primären Aperturstenosen nicht minder häufige während des Lebens erst erworbene. Wir sprechen kurz von der skoliotischen Aperturasymmetrie und Aperturstenose, welche auf einer primären Skoliose der oberen Brust- und Halswirbelsäule beruhen und sich als statisch-funktionelle Anpassungen an eine primär erworbene Anomalie der Wirbelsäule charakterisieren. An diesen sekundären Aperturanomalieen sind neben der Asymmetrie gleichfalls Rippen- und Knorpelkürze, Streckung der Rippe, Beeinträchtigung der seitlich-hinteren Aperturausbuchtungen die hervorstechendsten und für ihre pathogenetische Bedeutung massgebenden Merkmale. Im einzelnen kann ich nähere Ausführungen nicht machen, weil das viel zu weit führen würde, so beschränke ich mich denn darauf, hervorzuheben, dass diese sekundären Aperturanomalieen, die gleichfalls während der Entwickelung und namentlich gegen die Zeit der Reife zur Ausprägung kommen, deshalb so beachtenswert sind, weil wir in letzter Linie ihre Ätiologie in der Rachitis und vor allem in den Schädigungen während der Schulzeit zu suchen haben.

Das wird jedem ohne weiteres klar sein, der die Genese der habituellen Skoliose kennt.

Wenden wir nun unsere Lehre von der Stenose der oberen Thoraxapertur auf die Erscheinungsformen der tuberkulösen Lungenerkrankung an. Da haben wir zunächst als feststehende Tatsache vor uns, dass gerade zu der Zeit der Reife und in den folgenden Jahren, also zur Blütezeit des Lebens die tuberkulöse Lungenphthise besonders hereditär belastete Individuen befällt und in verheerender Weise jedes neu heranwachsende Geschlecht dezimiert. Liegt es nicht nahe genug, die hinlänglich bekannte fast sprungweise Steigerung der tuberkulösen Erkrankungsziffer gegen Ende des zweiten und während des ganzen dritten Lebensjahrzehntes mit den um diese Zeit zu absolutem anatomischen und funktionellen Missverhältnis führenden Aperturanomalieen in Zusammenhang zu bringen? Welcher Art dieser allein sein kann, haben wir gehört, und die Untersuchung eines grossen Leichenmateriales lehrt, dass, wenn nur eine genügend starke Infektion eintritt, durch die tuberkulöse Lungenphthise alle Träger stenotischer Aperturen ausgemerzt werden in scharfer, leider für die Verbesserung der Menschenrasse kaum in Betracht kommender Auslese. Nur selten finden sich bei alten Individuen typische Aperturstenosen. Finden wir für diese Anschauung eine Stütze schon in dem ausgesprochen individuellen Charakter der disponierenden Konstitutionseigentümlichkeit, da ja immerhin trotz fast allgemein gegebener Infektion ein nur kleiner Prozentsatz der Infizierten erkrankt und stirbt, so werden wir des weiteren bestärkt, um nicht zu sagen gewiss in unserer Ansicht, wenn wir die Lokalisation des primären tuberkulösen Lungenherdes namentlich auch in Hinsicht auf das Lebensalter des Individuums ins Auge fassen. Beim Erwachsenen beginnt die progrediente Lungenphthise fast ausnahmslos in der Spitze, und wir glauben ja auch dieses Lokalisationsgesetz erklären zu können. Liegt aber keine Aperturanomalie vor, sondern ein anderes disponierendes Moment, ein Trauma, Diabetes z. B., so ist auch der Sitz des primären tuberkulösen Lungenherdes ein durchaus atypischer. Gerade das merkwürdige anatomische Verhalten der Lungentuberkulose bei Diabetes, auf welches bisher nur v. Hausemann und ich hingewiesen haben, ist überaus lehrreich. Ein Individuum mit stenosierter oder starrer Apertur wird natürlich auch bei Diabetes eine typische Spitzenphthise acquirieren.

Als weiteres überaus wichtiges Argument für die Lehre der mechanischen Disposition der Lungenspitzen zur tuberkulösen Phthise kommt nun der allgemein bekannte Unterschied der tuberkulösen Lungenerkrankung bei Erwachsenen und bei Kindern hinzu. Beim Kinde finden Sie keine initiale Spitzenphthise, vielmehr vorwiegend eine Erkrankung vom Hilus aus, in den mittleren Lungenabschnitten. Hierfür eine in jeder Hinsicht genügende Erklärung zu geben, unbeschadet der Entscheidung, ob aërogene,

hämatogene oder lymphogene Infektion vorliegt, ist, wie ich glaube, mir allein bisher auf Grund meiner Lehre gelungen. Beim Kinde existiert die Disposition zur tuberkulösen Spitzenerkrankung noch nicht, aus mehreren Gründen: Die Natur der disponierenden Aperturanomalieen bedingt es, dass in frühen Lebensjahren die anatomischen Missverhältnisse keine auffallenden sein können, sondern erst zur Pubertätszeit, wenn alle Körperteile der endgültigen Vollendung entgegengehen, manifest werden. Dies gilt in erster Linie für die angeborenen Bildungsfehler, während es für die sekundären Anomalieen ja überhaupt keines Hinweises bedarf, dass sie im ersten Lebensdezennium kaum in Frage kommen. Wichtiger ist aber die Feststellung, dass schon deshalb im Kindesalter Aperturanomalieen keine Bedeutung für die Genese einer tuberkulösen Spitzenphthise haben können, weil die Lungenspitzen beim Kinde überhaupt noch nicht in räumliche Beziehung zum ersten Rippenringe getreten sind, dessen funktionelle Bedeutung ausserdem noch durch die Elastizität des kindlichen Brustkorbes zurückgedrängt ist. Die Apertur zeigt beim Kinde noch nicht die starke Neigung gegen die Horizontale wie beim Erwachsenen, vor allem aber sind die Lungenspitzen noch nicht im Wachstum nach oben in den ersten Rippenring hineingeschoben worden. Von diesen topographischen Verhältnissen kann sich ein jeder überzeugen, der die schön geformten hohen Pleurakuppeln am Thorax des Erwachsenen mit den flachen, fast planen des kindlichen Brustkorbes vergleicht. Mit einem Wort: Das Fehlen einer typischen initialen Spitzenphthise beim Kinde erklärt sich, steht man auf dem Boden der Lehre einer mechanischen Disposition der Lungenspitzen zur tuberkulösen Phthise, in jeder Hinsicht aus der Natur der disponierenden Faktoren und den topographischen Verhältnissen im Bereich der oberen Brustpartie. Eine funktionelle Störung kommt gar nicht in Betracht angesichts des vorwiegend auf der Thoraxelastizität basierenden kindlichen Atmungstyps.

Dass bei Kompression der Lungenspitzen sofort eine Disposition zur tuberkulösen Spitzenphthise auch beim Kinde eintritt, liess ich durch meinen Schüler Kitamura zeigen. Ein anomaler Verlauf der Arteria anonyma führte zur Furchenbildung, in deren Bereich eine Spitzentuberkulose in frühem Stadium festgestellt werden konnte. Wie hier, so sind überhaupt zufällige Befunde bei an interkurrenten Krankheiten und Unglücksfällen Verstorbenen besonders hoch zu veranschlagen, denn sie zeigen uns, was im weiteren Verlauf der Lungenzerstörung bis zur völligen Unkenntlichkeit verwischt wird.

Endlich noch eine Tatsache zur Stütze der vorgetragenen Lehre. Statistik wie persönliche Erfahrung lehren, dass im höheren Alter die Erkrankungsziffer an Tuberkulose gegen die mittleren Lebensjahrzehnte (40–60) wieder zunimmt. Die Stenose der Apertur kommt ätiologisch jetzt kaum

noch in Frage, wohl aber führt die immer mehr zunehmende Starrheit und Verknöcherung, welche im Gegensatz zur scheidenförmigen Verknöcherung als eine Alterserscheinung aufzufassen ist, immer mehr zur völligen Unbeweglichkeit des Rippenringes, welche ihren Ausdruck sogar in einer Verödung der Wirbelrippenverbindungen finden kann. Im Gegensatz zur progredienten uberösen tuberkulösen Lungenphthise junger Individuen sehen wir im Alter mehr die chronisch-fibröse Form, welche sich zu erklären scheint aus der verhältnismässig geringgradigeren Schädigung und ihrem langsameren Eintreten. Ja, was wir in den Lungenspitzen Jugendlicher nur selten sehen, wir finden überaus oft auch bei noch progredienter Tuberkulose ausgeheilte Herde oder solche, welche einer Ausheilung nahe sind. Die Natur zeigt sich hier als Lehrmeisterin für unsere therapeutischen Bestrebungen. Es kann sich nämlich am verknöcherten ersten Rippenknorpel ein Gelenk ausbilden, welches bis zu vollkommener Vollendung gedeihen kann. Eine solche Gelenkbildung an dem sonst fest mit dem Sternum verbundenen ersten Rippenknorpel, welche ursprünglich nichts anderes als eine unter der angestrengten Aktion der Skaleni zustande gekommene einfache Durchtrennung eines noch brüchigen, unvollständig verknöcherten Knorpels darstellt, ist nicht selten. Ihre häufige Koinzidenz mit ausgeheilten tuberkulösen Spitzenherden lehrt, dass die Immobilisierung des Rippenringes die Genese der tuberkulösen Spitzenerkrankung zum mindesten begünstigt haben muss. So dürfen wir aus der absoluten Zweckmässigkeit der Naturselbsthilfe rückschliessen.

Mit diesen leider nur skizzierenden Ausführungen muss ich mich begnügen, aber ich hoffe, dass auch aus dieser kurzen Mitteilung die Bedeutung mechanischer Missverhältnisse im Bereiche der oberen Thoraxapertur für die Genese einer tuberkulösen Lungenspitzenphthise klar hervorgegangen ist. Zugleich aber sei noch betont, dass die Anomalieen der oberen Thoraxapertur das anatomische, jederzeit sicherer empirischer Feststellung zugängliche Grundmoment darstellen, nach welchem wir den echten Thorax phthisikus zu bewerten haben. Meine diesbezüglichen gemeinsam mit Harrass niedergelegten Feststellungen zeigen, dass unter diesem Gesichtspunkte auch die heiss umstrittene Frage nach Wesen und Bedeutung des Thorax phthisikus einer einheitlichen Lösung entgegengeht.

Wie aber das Studium des Dispositionsproblems, speziell gewisser Anomalieen im Bereich der oberen Thoraxapertur uns tiefen Einblick in ein Gebiet der menschlichen Pathologie von allergrösster sozialer Bedeutung gestattet, eröffnet es uns andererseits lichtvolle Ausblicke hinsichtlich der Prophylaxe und Therapie der mörderischen Volkskrankheit "Tuberkulose." Es gilt, seitdem es gelang, an Stelle vager Begriffe reale anatomische, funktionelle und chemische Tatsachen zu setzen, neben dem Kampf gegen den Tuberkelbazillus energisch auch den gegen die nicht weniger bedeutsame

Disposition aufzunehmen. Wie schon F r e u n d vor 60 Jahren ausführte, zeigt uns die Natur selbst den Weg. In gewissen Fällen von tuberkulöser Spitzenphthise geringer Ausbreitung ist die operative Durchtrennung der starren ersten Rippenknorpel zu fordern. Doch liegt es nahe, von dieser Operation, welche ein gutes funktionelles, selten aber ein anatomisches Resultat haben wird, nicht allzuviel zu erwarten und sie besonders auf die Altersverknöcherung des ersten Rippenknorpels anzuwenden. In Deutschland haben Kausch und Seidel anscheinend mit gutem Erfolge in jüngster Zeit die Operation ausgeführt. Allein weit wichtiger scheint es, prophylaktische Massnahmen zu ergreifen, um den Ausbruch eines Feuers zu verhindern, das später schwer zu löschen ist. Hier ruft die Pflicht Eltern, Lehrer und sozialhygienischen Gesetzgeber auf den Plan. Neben der ständigen Besserung allgemeiner Hygiene steht die Bekämpfung der Syphilis und des chronischen Alkoholismus obenan. Dem Kinde, namentlich dem schwächlichen, ist dauernde Aufmerksamkeit zu widmen, die Dehnung und Kräftigung der Brust ist durch systematische Atemübungen und planvollen Turnunterricht zu fördern, in der Schule für eine gesunde und zweckmässige Sitzgelegenheit zu sorgen und die Ausbildung einer Skoliose der obersten Brustwirbelsäule in jeder Weise, eventuell durch Einführung der Keilschrift zu verhindern. Die schulentlassene Jugend ist möglichst durch obligatorische Turn- und Freiübungen auch ferner in ihrer körperlichen Entwickelung zu fördern. Das sind so die Grundgedanken der prophylaktischen Massnahmen; sie auszubauen muss unser Bestreben sein, denn die Verhinderung der Ausbildung pathologischer Thoraxformen ist die beste Unterstützung im Kampfe gegen den Tuberkelbazillus selbst, dessen Ansiedlung, Anreicherung und Verbreitung sie verhindert.

The Predisposition of the Lung Apices to Tuberculosis.—(HART.)

1. Aside from infection, the cause of pulmonary tuberculosis in youthful individuals is to be sought in an individual predisposition due to anatomical and functional disturbance of the normal conditions around the superior aperture of the thorax.

2. These improper conditions may be congenital, hereditary, or acquired during life.

3. The predisposition is at first purely local. Actual and functional diminution of the pulmonary apices not only favors the deposition of tubercle bacilli, but also diminishes the natural powers of resistance inherent in the tissues.

4. This predisposition determines the localization of the first tuberculous focus in the pulmonary apices.

5. Local predisposition is equally significant for air, blood, and lymphatic infection.

6. The final outcome of the battle between the tubercle bacilli and the tissues depends on the degree of this anatomical and functional disturbance in the region of the superior aperture of the thorax.

7. Children do not exhibit this predisposition of the pulmonary apices to tuberculosis.

8. In older individuals (of the age of fifty and over) the predisposition is caused almost exclusively by inhibition of the function of the superior aperture of the thorax, due to senile changes.

9. The measures to be employed in combating tuberculosis should be directed, more than has been done in the past, against the development of an individual predisposition.

VERERBUNG IN DER SCHWINDSUCHTSFRAGE.

Von Dr. S. v. Unterberger,
St. Petersburg.

Solange die Schwindsucht als solche erkannt, studirt, und therapeutisch Beachtung gefunden, so lange existirt auch die Frage über ihre Entstehung, ob sie durch Vererbung oder durch Ansteckung sich verbreitet. Letztere Anschauung ist jetzt wieder die herrschende.

In den letzten Decennien sind die biologischen Forschungen über Entwickelung der Geschlechtszellen sehr zahlreichen Untersuchungen unterworfen und haben aufklärend eine Fülle von neuen Anschauungen aufzuweisen, die im Stande sind, auch die Gegensätze zwischen Hereditarier und Infektionisten auszugleichen. Im Grunde ist ja zwischen den Infektionisten und Hereditariern kein wesentlicher Unterschied, sondern nur ein gradueller, je nachdem die einen mehr auf den Boden, die andern mehr auf die Infektionskeime Gewicht legen.

Welche Ergebnisse hat nun aber die Entwickelungs-Mechanik aufzuweisen?

In der Befruchtung der Eizelle erblicken wir jenen für die Vererbungslehre bedeutungsvollen Vorgang, durch welchen väterliche und mütterliche Qualitäten in einem Individuum vereinigt werden. Als materielles Substrat dieses Prozesses—von Weismann Amphimixis bezeichnet—stellt sich uns die Vereinigung zweier Zellkerne dar, des Spermakernes mit dem Eikern.

Wenn wir den geheimnissvollen Erscheinungen der Vererbung näher zu treten versuchen, schreibt Heider, so stehen zwei Wege offen, auf denen mit Aussicht auf Erfolg vorzudringen möglich wäre. Der erste Weg bedient sich der planmässigen Züchtungsexperimente. Durch genauere Feststellung der Merkmale, welche die einzelnen aus einander hervorgehenden Generationen erkennen lassen, werden wir zu allgemeineren Vorstellungen über die Art ihrer Uebertragung geführt und wir werden veranlasst, einzelnen Merkmalen alsdann eine erhebliche Selbstständigkeit zukommen zu lassen, indem sie in den mannigfaltigsten Kombinationen in die Bildung der Keimzellen eingehen können. Erscheint uns so der ausgebildete Organismus als ein Bündel von Merkmalen oder von elementaren Eigenschaften, wie De Vries sie benennt, so werden wir dazu geführt, für jede derselben besondere repräsentative Teilchen in der Keimsubstanz zu postulieren.

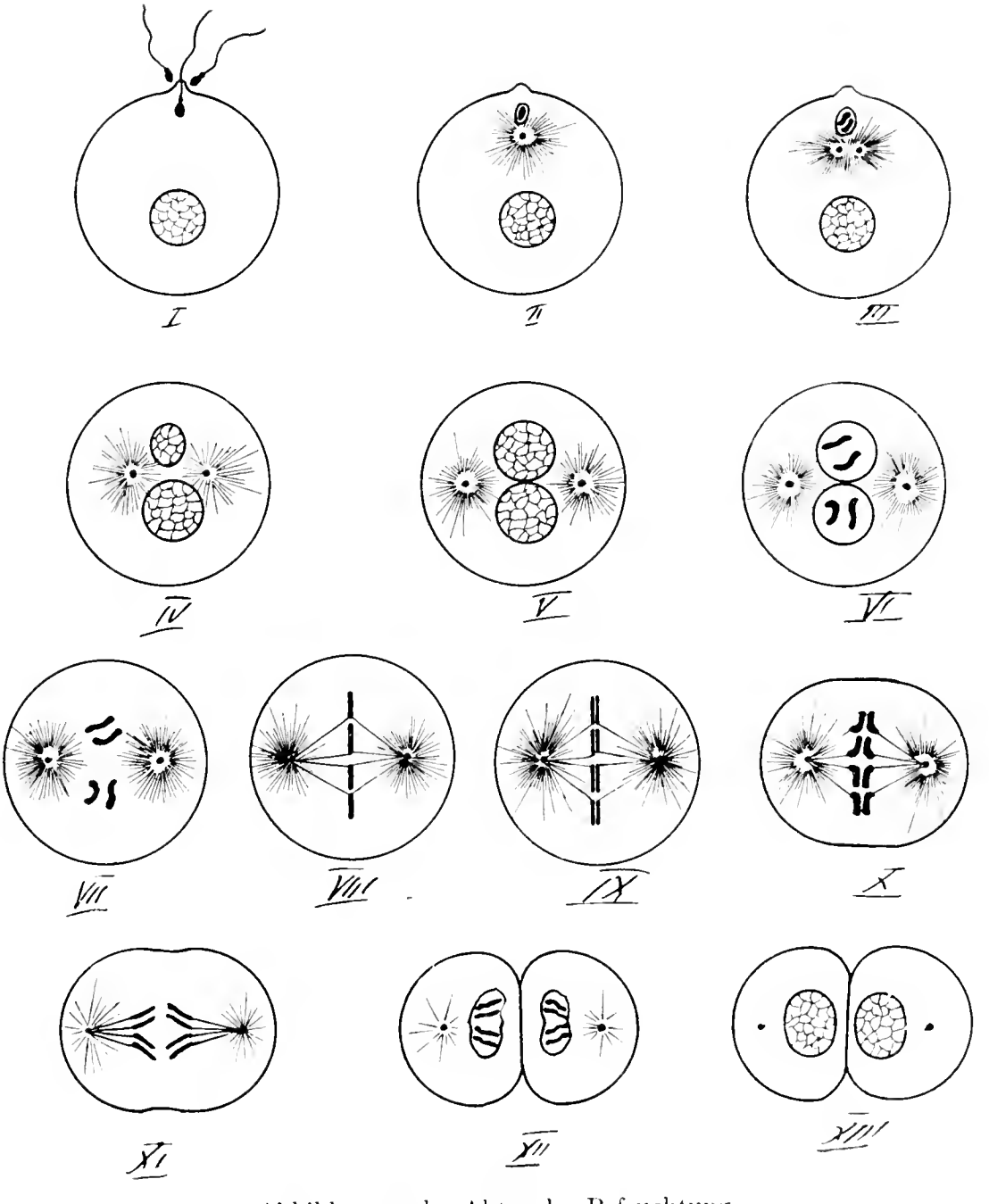
Diese repräsentativen Teilchen der Keimessubstanz näher kennen zu lernen führt uns zur Betretung des zweiten Weges, zur Erforschung der cytologischen Grundlage der Vererbungserscheinungen. Auf dem Standpunkte der Zellentheorie stehend, müssen wir in letzter Linie die Phänomene der Vererbungserscheinungen in den Vorgängen des Zellenlebens erblicken.

Erscheint der Organismus als ein Bündel von Merkmalen, so werden wir dazu geführt, für jedes derselben eine besondere Anlage in der Keimsubstanz zu postulieren.

Abbildungen des Aktes der Befruchtung, welcher die Vererbung illustrirt auf Grund von Arbeiten von Boveri, Hertwig, Heider, und anderen.

Bild I.—Die höheren tierischen Organismen vermehren sich und wachsen ebenso, wie die niederen, und ebenso, wie die pflanzlichen, vermittelst Teilung der Zellen. Die Zelle ist die Basis einer jeden Organisation und die Teilung der Zelle ist die Basis einer jeden Vermehrung. Die Zelle, deren Bau bis in die kleinsten Details noch nicht endgiltig aufgeklärt ist, besteht aus einem Klümpchen lebender Materie, genannt Protoplasma, und aus einem im Innern sich befindlichen Kern. Eizelle oder Ei, aus dem sich der complicirte Organismus entwickelt—miteingerechnet auch den menschlichen—stellt ebenso dar (Bild I) ein Klümpchen Protoplasma und im Innern einen Kern. Diesen Kern bezeichnet man als Eikern. In demselben kann man unterscheiden in der Mitte der Hülle ein feinfaseriges Netz, welches die Fähigkeit besitzt, in sich verschiedene Farben aufzunehmen. In Folge dessen bezeichnete man es als Chromatinnetz. Auf diesem und den folgenden Bildern ist das Chromatinnetz des Eikerns mit blauer Farbe gefärbt. Weiter sieht man auf dem Bilde in dem Empfängnisshügel des weiblichen Eies das Eindringen des männlichen Eies, dem Spermatozoiden, welcher zusammengesetzt ist aus einem Kopf (roth gefärbt) und einem Schwanz. Darin besteht nun der Akt der Befruchtung. Man hat ausserdem beobachtet, dass der Eihügel sich nicht passiv verhält, sondern nach allen Richtungen sich dreht zu dem ihn umschwärmenden Spermatozoiden.

Bild II.—Sobald der Spermatozoide ins Ei gedrungen, d. h. sobald der Akt der Befruchtung erfolgt ist, so verliert er den Schwanz und von diesem Moment an stellt er vor den Spermakern. Auf diese Weise bestehen in befruchteter weiblicher Eizelle zwei Kerne: ein grösserer (blauer) und ein kleinerer Samenkern (rother). Gleich von vornherein ist der Samenkern bedeutend kleiner als der Eikern. Alles wesentliche, jeder nothwendige Vorrath an Materie und Energie ist hier enthalten, aber wie in gepresster und concentrirter Form. Durch diesen Umstand werden erleichtert die lebhaften Bewegungen, die für den Spermatozoiden nöthig sind. Zu dieser Zeit des geringen Vorrathes an Protoplasma im Samenkern, aus dem Vorrath, welchen es mit sich genommen in die Eizelle, trennt sich auch ein neuer Körper ab, der sich vor den Samenkern lagert, zwischen ihm und dem



Abbildungen des Aktes der Befruchtung.

Eikerne. Dieser Körper ist dargestellt durch einen schwarzen Punkt umgeben von Strahlen, die sich um ihn verbreiten, ähnlich wie sich um die Pole eines Magneten Eisenfeilspäne gruppiren. Das ist der Centralkörper oder Centrosom.

Bild III.—Die Eizelle ohne sichtbare Veränderungen; Samenkern ist vergrössert und es beginnt sich zu bilden ein ähnliches (roth gefärbt) Chromatinnetz, wie der Eikern. Er hat sich dem Eikerne genähert. Das Centrosom hat sich geteilt in zwei schwarze Punkte umgeben von Strahlen.

Bild IV.—Das Chromatinnetz des Samenkerns ist grösser, deutlicher; der Samenkern selbst ist grösser geworden und hat sich noch mehr genähert dem Eikerne, der sich seinerseits auch vergrössert hat. Zwei Chromosome sind vollständig gesondert und gehen auseinander, das eine rechts, das andere links, gleichsam zwei Pole bildend.

Bild V.—Der Samenkern hat dieselben Grössen erreicht, wie der Eikern, und nach seinem Äussern und feinsten Bau ähnelt er ihm vollkommen. Zu gleicher Zeit haben sich beide Kerne genähert bis zur Berührung, in einzelnen Fällen sogar vielleicht bereits verschmolzen in einen Kern. Wir haben hier vor uns gleichsam eine neue Befruchtung, eine Befruchtung der Kerne. Die Chromatinnetze beider Kerne sind scharf bestimmt. Beide Centrosome haben sich bedeutend vergrössert und treten deutlich ausgesprochen auf: das eine auf der rechten, das andere auf der linken Seite. Von diesem Moment an beginnt ein höchst interessanter Akt, der wahrscheinlich sich schon früher vorbereitete und auf dem nächsten Bilde dargestellt ist.

Bild VI.—Die Fäden des Chromatinnetzes fangen an sich zusammenzuziehen; in jedem Kerne, im männlichen wie im weiblichen, erscheinen Stäbchen, häufig gekrümmt, die in sich die ganze Chromatinsubstanz aufnehmen, so dass auf der übrigen Fläche des Kernes von früher gefärbten Netzen keine Spur nachbleibt. Diese Stäbchen heissen Kernschleifen oder Chromosome. Die grosse Bedeutung der Chromosome besteht darin, dass in ihnen sich die Vererbung vollzieht. In diesen Stäbchen concentrirt sich die ganze Summe des vererbbaren Vorraths an Materie und Kraft, die von unzähligen Vorfahren übergeht in das neu entstandene Wesen. Dabei ist noch bemerkenswerth der Umstand, dass für jede Art des Organismus eine bestimmte Zahl von Chromosomen existirt,—das Gesetz der Zahlenconstanz. Wenn z. B. für unser Individuum, wie beifolgende Zeichnung zeigt, charakteristisch sind vier Chromosome, so werden zwei von ihnen dem männlichen Kerne und zwei dem weiblichen angehören. Es giebt Arten mit 12, 16, 24 Chromosomen, u. s. w.

Centrosome auf unserer Zeichnung sind wie früher von beiden Seiten der Kerne gelagert, die in der Mittel- oder Aequatoriallinie sich befinden.

Bild VII.—Vier Chromosome haben sich vollständig befreit von dem

sie umgebenden Protoplasma und der Kernhülle und haben sich gleichsam entblösst.

Bild VIII.—Hier sehen wir, dass die so zu sagen entblössten Chromosome sich in Reih und Glied gestellt auf der charakteristischen Spindelfigur mit den Strahlensonnen (Chromosome) an ihren Polen.

Bild IX.—Wir haben den Akt der Befruchtung verfolgt bis zur vollständigen Bildung von männlichen und weiblichen Chromosomen und bis zu ihrer Bildung etwa einer Schlachtlinie. Jetzt beginnt die Vorbereitung zur Teilung der Zelle, d. h. zur Verwandlung eines Individuums in ein anderes. Der erste Akt dieser Teilung besteht in einer Teilung jedes Chromosoms in zwei: unsere Schlachtlinie hat sich geteilt in zwei; aus vier Chromosomen haben sich acht gebildet, aus einer Schlachtlinie zwei und jeder Schlachtlinie wieder vier Chromosome, zwei männliche und zwei weibliche. Folglich werden die zukünftigen zwei Tochterzellen jede, wie die Mutterzelle, vier Chromosome haben: zwei männliche und zwei weibliche.

Bild X.—Die Chromosome fangen an, angezogen zu werden durch die Strahlen der Centrosome, und zwar die rechte Reihe durch die Strahlen des rechten, die linke durch die Strahlen des linken Centrosoms.

Bild XI.—Das Anziehen schreitet vorwärts, und in der Nähe jedes Centrosoms sammeln sich ebenso viele Chromosome, wie viel es ihrer anfänglich in der Mutterzelle gab. Zugleich vergrössert sich die Zelle in die Breite, und das Protoplasma beginnt sich zu teilen.

Bild XII.—Die Strahlen, die das Centrosom umgeben und die mit ihm sich bildende sternförmige Figur, haben ihre Rolle ausgespielt und verschwinden. Auf jeder Hälfte umgeben sich die Chromosome mit Protoplasma und einer Hülle und bilden einen Tochterkern. Die Eizelle fährt fort sich zu teilen in zwei.

Bild XIII.—Die Mutterzelle hat sich vollständig getrennt in zwei Tochterzellen. Die Chromosome sind geschwunden in dem Chromatinnetz, wobei jeder Tochterkern das Resultat darstellt von einer Verschmelzung des Samenkerns mit dem Eikern der Mutterzelle. Auf diese Weise enthält jeder neue Kern ebenso viel männliche wie weibliche Materie. Mit anderen Worten, im zukünftigen Organismus des Kindes befindet sich annähernd die Hälfte des väterlichen und die Hälfte der mütterlichen Materie und Energie.

Darin liegt das Geheimniss der Vererbung.

Scheint nicht in dieser einheitlichen Tätigkeit des männlichen und weiblichen Kerns die Natur auszeigen zu wollen, gleichsam wie ein Symbol, die sociale Gleichberechtigung beider Geschlechter?

Hier muss angeführt werden folgender für die Entwickelungs-Mechanik wichtige Vorgang. Die beiden in der Befruchtung sich vereinenden Kerne enthalten nur je die halbe Zahl von Chromosomen, so dass erst durch ihre

Vereinigung wieder ein vollwertiger Kern mit der ganzen Normalzahl von Bestandteilen geschaffen wird. Die Herabsetzung der Zahl der Chromosome auf die Hälfte erfolgt in der Reifungsperiode der Keimzellen. Dieser spezielle Teilungsmodus wird als Reduktionsteilung bezeichnet.

Für die Vererbungslehre ist demnach erstens die Tatsache von Wichtigkeit, dass die Samen und Eizelle, obgleich sehr verschieden ausgerüstet—die Eizelle durch Anhäufung plastischen Materials erheblich umfangreich, die Samenzelle klein, compendiös—doch zwei gleichartige Bestandteile, die Geschlechtskeime, enthalten, in deren Vereinigung das für die Vererbung wichtigste Moment zu erblicken ist. Zweitens, dass bei der Befruchtung die gleiche Zahl von Kernschleifen oder Chromosomen väterlicher und mütterlicher Provenienz zusammentreten um den ersten Furchungskern zu bilden, und dass bei der nachfolgenden Ontogenese dieselbe Zahl auf die Nachkommen weiter übertragen wird.

Durch diese Tatsache schien die Uebertragung der Eigenschaften beider Eltern auf das Kind bis zu einem gewissen Grade erklärt. Und wenn man der Annahme hinzufügt, dass bei der Ausbildung des Kindes diese beiden in jeder Zelle deponierten Erbmassen nicht immer in gleicher Kraft wirksam seien, weil die Chromosome sich als qualitativ verschieden erwiesen, und somit gelegentlich die eine über die andere einen überwiegenden Einfluss geltend macht, so schien auch die Tatsache erklärlich, dass die Kinder häufig in gewissen Merkmalen mehr oder ausschliesslich dem einen der beiden Eltern nachgeraten (Heider).

Wenn wir die Chromosome als den Träger der Erbmasse im allgemeinen bezeichnen, so fragt es sich, ob es nicht jetzt schon möglich ist, die Chromosome in einzelne Komponenten zu zerlegen. Den Chromosomen kommt entschieden eine gewisse Selbstständigkeit zu, ja sie präsentieren sich uns als bestimmt organisierte Bestandteile des Keims, ja förmlich als selbstständige kleine Organismen, die in ihrem Bau an Bakterien erinnern.

Man hat bei einigen Organismen beobachtet, schreibt Heider, wie zwei Chromosome sich einander nähern; sie scheinen durch einen geheimnissvollen Trieb, durch eine uns rätselhafte Anziehungskraft an einander geführt, bis sie sich berühren und schliesslich zu einer Gruppe vereinigen. Dieses Sichaufsuchen und Vereinigen zweier Chromosome, die im ganzen übrigen Leben des Organismus getrennt waren, erinnert an die Vorgänge der Konjugation bei einzelligen Wesen und man hat auch hier von einer Konjugation der Chromosome gesprochen. Ob bei den gewöhnlichen Konjugationen, wie bei den Infusorien, in denen nachträglich die Konjugationen sich wieder von einander trennen, ein Austausch chromosomer Substanz stattfindet, dafür liegen noch keine Beobachtungen vor, doch diese Annahme wird wohl noch ihre Bestätigung finden.

Da nun die Chromosome nur in bestimmten Zuständen des Zellkernes zu

erkennen sind, nämlich dann, wenn er sich zur Teilung anschickt, während sie in der übrigen Zeit in dem gleichmässigen Kerngerüste nicht wahrnehmbar sind, so können wir zunächst nur den Schluss ziehen von einer Erhaltung der Individualität der Chromosome; und eine weitere Reihe von Tatsachen, die für die Erhaltung der Individualität der Chromosome spricht, ist das Gesetz der Zahlenkonstanz der Chromosome, wobei neuerdings festgestellt ist, dass einzelne Chromosome sich von den übrigen unterscheiden lassen, sei es, dass sie grösser oder kleiner sind, sei es, dass sie sich durch ihr färbbares Verhalten auszeichnen.

Da wir mit Wahrscheinlichkeit annehmen dürfen, dass jedes Chromosom aus mehreren möglicherweise zahlreichen qualitativ verschiedenen Teilchen zusammengesetzt ist, so liegt die Versuchung nahe, über die Struktur der Vererbungssubstanz, über ihren Aufbau aus kleinen, individualisierten Anlagen, die Weissman Determinanten bezeichnet hat, uns bestimmtere Vorstellung zu bilden. Die Versuchung liegt um so näher, als man ja eine Zusammensetzung der Chromosome aus kleinen Partikelchen, sogenannten Mikrosomen, zu beobachten schon in der Lage ist. Von der Rolle dieser kleineren Partikelchen für die Vererbung sind wir derzeit nicht im Stande etwas sicheres auszusagen. Dagegen suchen wir, sagt Heider, auf wohlbegründetem Boden, wenn wir uns darauf beschränken, die Rolle der Chromosome ins Auge zu fassen und in ihnen selbstständige, individualisierte und qualitativ verschiedene Träger erblicher Eigenschaften zu erblicken.

Wenn man nun bedenkt, dass die höheren Organismen sehr hohe Chromosomenzahlen aufweisen, so steigt hiermit die Zahl der möglichen Kombinationen ins Ungeheure. Durch die Reifungsteilung wird nun das Erbgut an grosselterlichen Chromosomen den Enkeln in den mannigfaltigsten Kombinationen übermittelt und dabei sichert doch jede Keimzelle die vollständigen zur normalen Entwickelung nötigen Chromosomengarnituren. Es erklären sich auf diese Weise die oft auffallenden Unterschiede zwischen Geschwistern und die launenhaften Uebertragungen der grosselterlichen Anlagen, die besonders bei hereditären Dispositionen zu Krankheiten oft bemerkt werden (Heider).

Wie wir sehen, sind die neuesten Forschungen auf dem Gebiete der Entwickelungs-Mechanik aus dem Bereiche der Hypothesen getreten und wir fangen an, Fuss zu fassen auf Tatsachen. Diese zytologischen Forschungen ergänzen sich zudem bereits in vielen Stücken durch verschiedene Züchtungsversuche. Wie gering die gewonnenen Tatsachen aber auch sind, sie geben doch schon eine Handhabe, uns klare Begriffe zu machen auch über die Vererbung der Schwindsucht, oder exakter ausgedrückt, über die Vererbung der Anlage zur Schwindsucht. Zur Lösung dieser wichtigen Frage sind aber auch wir praktische Aerzte in hohem Grade im Stande, fördernd zu wirken, und zwar durch systematische Aufstellung von Ahnentafeln. Riffel

hat bereits ein schönes Material dazu geliefert, indem er kleine Orte zum Gegenstande seiner Studien wählte und eine Zusammenstellung der Todesursachen bei den Einwohnern durch mehrere Generationen in der Ascendenz in mühevoller Weise zusammengebracht hat. Riffel's Arbeiten wurden seinerzeit unter dem einseitigen Einfluss der Bakteriologen nicht genug gewürdigt. Erst in jüngster Zeit, veranlasst durch die hervorragenden Studien über Pathogenese der inneren Krankheiten von Prof. Martius, fangen seine Arbeiten an immer mehr zur Geltung zu kommen.

Es ist das Verdienst des Historikers Prof. Lorenz, wie Martius es hervorhebt, dass wir einen neuen Weg der Verwendung der Ahnentafeln betreten haben, um in der Frage der Erblichkeit pathologischer Anlagen weiter zu kommen. Schlüter hat aus den wertvollen Arbeiten von Riffel Ahnentafeln zusammengesetzt, wo die gesammte Erbmasse des Einzelindividuums ganz und voll zum Ausdruck kommt. In den Ahnentafeln steckt die ganze Erbmasse des als Ausgangspunkt gewählten Individuums, die weiblichen Ahnen sind vollständig darin enthalten, während bei den Stammbäumen nur solche Mitglieder verzeichnet sind, die denselben Familiennamen führen.

Schlüter führt aus der Riffel'schen Arbeit nur vier Beispiele an und stellt in diesen schon recht vollständige Ahnentafeln zusammen, die bis zu 62 Ahnen durch 5 Generationen aufweisen. Wie wir früher gesehen, sind die Dörfer, die Riffel beschrieben, stark verseucht bei vollständig antisanitären Verhältnissen, so dass eine ganz aussergewöhnliche Exposition für jeden Insassen vorhanden ist. Z. B. die Familie Weick, in Tafel I, war einer Infektion besonders stark exponiert und wird einer öftern Infektion schwerlich entgangen sein; sie blieb durch 5 Generationen in Bezug auf Schwindsucht verschont. In andern Tafeln kann man deutlich verfolgen, wie die phthisische Belastung forterbt oder wo die nichtbelasteten verschont bleiben.

Die Konstitutions-Pathologie, auf die Hüppe als erster mit Nachdruck aufmerksam gemacht, stellt somit die Rolle der Heredität bei der Krankheitsentstehung in das rechte Licht. Andere Ursachen können nur da Krankheitsvorgänge auslösen, wo sie eine entsprechende spezifische Anlage vorfinden.

Welche Begriffe existieren aber immer noch unter Aerzten über Vererbung und Anlage in der Pathologie der Phthise?

Während Koch im Jahre 1884 vorläufig die Annahme einer Disposition noch bestehen zu lassen meint, erklärt er auf dem Londoner Kongress vor wenigen Jahren, dass die erbliche Tuberkulose doch praktisch gar keine Bedeutung habe. Die Disposition giebt Koch zu, die Erblichkeit leugnet er, sagt Martius. Wie verhalten sich nun aber Disposition und Vererbung zu einander?

Wenn es Phthisikerfamilien giebt, die von Hause aus eine verringerte Widerstandskraft gegen den Tuberkelbazillus mit auf die Welt bringen, so muss

diese besondere Disposition oder Anlage auch ererbt sein; sie muss, um in der Sprache der Biologie zu reden, in bestimmten Determinanten oder Determinantengruppen gegeben sein, die diesem Individuum in seiner Erbmasse mitgegeben sind. Es ist biologisch unmöglich, die Bedeutung der Veranlagung für die Phthisegenese zuzugeben und doch die Rolle der Vererbung nicht sehen zu wollen. Dieser scheinbare Widerspruch erklärt sich aber sofort, wenn es nun klar wird, dass Koch nicht an die Vererbung im exakt biologischen Sinne gedacht, sondern lediglich die germinative event. plazentare Infektion im Auge gehabt hat. Auch Behring spricht sich nicht biologisch exakt aus, wenn er von prägenitaler und postgenitaler Heredität spricht. Gemeint ist wiederum nicht Vererbung, sondern Infektion.

Was versteht nun die Biologie unter Vererbung im Allgemeinen?

Unter ererbt versteht die Biologie nur solche Eigenschaften oder materielle Substrate, die als Anlagen im Keimplasma der elterlichen Geschlechtszellen enthalten waren. Die ganze Erbmasse des neuen Individuums steckt materiell in den beiden nach dem Kopulationsakte miteinander verschmelzenden Geschlechtszellen—dem Ei und dem Spermatozoon. Ist diese Verschmelzung geschehen, so ist der Akt der Vererbung vollendet. Angeboren (kongenital) ist also alles, was ein Kind mit auf die Welt bringt. Ererbt ist aber nur das, was aus den Determinanten der beiden Geschlechtszellen sich entwickelt. Intrauterine Erwerbungen sind somit als angeboren zu bezeichnen, nicht als ererbt.

Das Anlagekapital an geistigen und körperlichen Eigenschaften und Fähigkeiten an Eigentümlichkeiten krankhafter oder gesundhafter Art, das ein jeder von uns mit auf die Welt gebracht hat, verdankt er beiden Eltern zu gleichen Teilen. Seinen direkten embryologischen Ausdruck findet dieses biologische Postulat in der Tatsache, wie wir gesehen, dass nach Teilung der Chromatinfäden—durch Reduktionsteilung—die Hälfte eines jeden Kernes der beiden Geschlechtszellen mit der Hälfte des andern zu je einem neuen Kern sich vereinigt, so dass nunmehr in der gemeinschaftlichen Protoplasmamasse zwei neue Kerne sich dann bilden, von denen jeder ebenso viel Material vom männlichen Spermatozoon besitzt, wie vom weiblichen Ei. Und so geht die Teilung weiter. Daher kommt es, dass in dem neuen aus dem Ei sich entwickelnden Tiere in allen Zellen seines Körpers gleichviel Chromatin (Keimsubstanz) väterlichen wie mütterlichen Ursprunges enthalten ist. Das neue Wesen ist in allen seinen Teilen und künftigen Eigenschaften fest bestimmt. Der Einfluss der Mutter, der von nun an allein wirksam wird, kann daher nur ein modifizierender, die Entwickelung hemmender oder fördernder sein. Aber es kann der nun fixirten Erbmasse nichts neues, keine Determinanten mehr hinzufügen.

Die Krankheitsdeterminanten, die jeder einzelne von uns in wechselnder Zahl, Art, und Kombination aufweist, stammen, wie alle seine Determinan-

ten überhaupt, aus seiner ihm individuell zugehörigen Ahnenmasse. Was in dieser nicht vorgebildet ist von weiter vererbbaren Anlagen (Determinanten), das bringt kein äusserer Einfluss mehr in das nach der Kernverschmelzung gegebene und fest begrenzte individuelle Keimplasma hinein.

Die individuellen Differenzen setzen Determinanten voraus, die im Ahnenplasma der Eizellen vorhanden sein können, aber nicht müssen; je höher organisiert die ganze Gattung, desto grösser die Zahl dieser individuell wechselnden Determinanten. Wenn die Genealogie lehrt, dass jeder Mensch in der siebenten Generation aufwärts schon 128, in der achten 256, in der zwölften bereits 4096 Ahnen gehabt hat, die alle individuell verschieden waren und von denen allen er eine oder mehrere besondere individuelle Determinanten geerbt haben kann, so begreift sich die ungeheure Zahl individueller Kombinationen, die bei seiner eigenen Zeugung möglich war en, von denen aber nur eine sich realisiert hat.

Der Begriff der erblichen Belastung wird meist viel zu eng gefasst. Nicht die Tatsache allein, ob eines der Eltern oder beide an der gleichen Krankheit gelitten haben, wie der Explorand, ist entscheidend. Auf dieser engen Basis aufgebaute Statistiken bringen uns allein wissenschaftlich nicht weiter. Alle krankhaften Anlagen, die bei irgend einem Individuum hervortreten, sind als ererbte anzusehen, ganz gleichgiltig, ob die entsprechenden Krankheiten bei den Eltern oder deren Vorfahren nachweisbar sind oder nicht.

Die latente Vererbung spielt nämlich in der Pathologie eine viel grössere Rolle, als gewöhnlich angenommen wird. Nur ist es bei der Unsicherheit unserer genealogischen Familienkenntnisse auch nur über die nächsten Generationen hinaus meist sehr schwer, den Nachweis zu führen, bei welchen der zahllosen Ahnen die entsprechende Determinante zur Entwickelung gekommen ist.

Die Frage nach der Vererbung pathologischer, wie auch normaler psychischer und leiblicher Charaktere läuft nun aber einfach auf eine Wahrscheinlichkeitsrechnung hinaus. Kein vernünftiger Mensch, sagt Martius, glaubt an die Möglichkeit eines Systems, mit dem es gelingen müsse, in Monte Carlo mit Sicherheit vorauszuberechnen, ob im Einzelfalle die Kugel auf rouge oder noir oder gar auf Zero fällt. Was wir wissen, ist nur dass die Wahrscheinlichkeit für rot sich wie 1 zu 2, für Zero aber nur wie 1 zu 36 verhält. Ungefähr mit ähnlicher Wahrscheinlichkeit wissen wir, dass für ein Elternpaar seine Kinder mit dem komplizierten Determinantenkomplex, den wir "ausgesprochene phthisische Anlage" nennen, um so geringer, je weniger Phthise in der beiderseitigen Ahnenmasse auszufinden ist. Dabei ist aber keineswegs gesagt, dass aus einer tuberkulös stark belasteten Ahnenmasse im Einzelfalle ein besonders widerstandsfähiges Individuum hervorgehen kann. Wer Pech hat, sagt Martius, erwischt bei der Kernver-

schmelzung, aus der er hervorging, selbst die einzige schwarze Kugel (d. h. Krankheitsdeterminanten) die in seiner Ahnenmasse steckte, während ein anderer fast nur aus weissen Kugeln entstand.

Die neuesten Forschungen haben unter anderem noch gezeigt, dass bei der Befruchtung das Ei nicht die passive Rolle spielt, die ihm früher zugeschrieben wurde. Die biologischen Forschungen zeigen ein deutliches aktives Verhalten des Befruchtungshügels, man sieht wie derselbe sich nach allen Seiten hin richtet, wo die Spermatozoen an ihn heranrücken. Wie im gewöhnlichen Leben nicht selten Schwindsuchtskandidaten eine gewisse Zuneigung zeigen, so könnte das auch bei den sich befruchtenden Ei- und Spermazellen nicht unmöglich sein. Unter der stattlichen Zahl von über 50 Millionen Spermatozoon-Bewerbern, die ja bei einer Ejakulation ausgeworfen werden sollen, könnten gerade die Tuberkuloseveranlagten mehr Neigung zu einander empfinden. Sehen wir nicht sehr viele Aborte bei Schwindsüchtigen, wo bei der Kopulation die Anlage bei den einzelnen akkumuliert, rasch zum Untergange des zukünftigen Individuums führen, und zwar bereits im Uterusleben? von der grossen Sterblichkeit in den ersten Lebensjahren schon nicht mehr zu reden.

Wir können jetzt nicht mehr leugnen die Existenz einer Anlage, einer Disposition für Schwindsucht. Die Disposition ist nicht etwas in der Luft Schwebendes, sie muss irgendwo ihren Sitz haben, d. h. ein Substrat, in dem sie sich entwickelt und abläuft. Krankhafte Störungen oder krankhafte Veränderungen ohne anatomischen Sitz giebt es nicht. Diesen anatomischen Gedanken Virchows dürfen wir bei Besprechungen der Pathogenese der Krankheiten nie vergessen, nie aus den Augen lassen.

Wichtig ist jetzt nur die Frage zu entscheiden, welches denn eigentlich die Gewebszellen sind, an welche die spezifisch tuberkulöse Anlage gebunden. Entgültig ist diese Frage immer noch nicht entschieden, doch scheinen die neusten Arbeiten, so unter anderem die Arbeiten von Weleminsky dafür zu sprechen, dass die Tuberkelknötchen sich stets im Lymphsystem entwickeln. Von Alters her ist die "lymphatische Konstitution" eng verbunden mit der Schwindsucht und wir sehen ja meist auch das Lymphsystem bei der Phthise ergriffen. Der Tuberkel wird ja auch als Lymphom von Virchow bezeichnet.

Die Anlage zur Phthise stellt nicht eine spezifische Determinante dar, sie setzt sich vielmehr in jedem Falle aus einer ganzen Reihe an sich variabler anatomisch-physiologischer Faktoren zusammen, die nach Menge und Ausprägung den grössten Schwankungen unterliegen und sich bald so, bald so kombinieren können. So ist mehr oder weniger schliesslich jeder disponiert, aber es bestehen ja nach Menge, Hochgradigkeit und zufälliger Kombination jeder Einzelmomente zwischen den einzelnen Individuen bedeutende Unterschiede in der Widerstandskraft gegen die Wirkung der tuberkulösen Infektion—von den geringsten bis zu den stärksten Graden der phthisischen

Veranlagung in zahllosen Abstufungen und Kombinationen (Schlüter, Martius).

Wenn wir das Lymphsystem für den anatomischen Sitz der Tuberkulose halten müssen, so erklärt sich leicht das vielfältige Bild derselben in allen Organen, da alle Organe Lymphgefässe besitzen. Bei der Anlage wird beim Kinde das krankhaft disponierte Lymphsystem nicht gleichmässig, sondern bald in einem, bald in dem andern Organ vererbt und wir sehen, dass Tuberkulose bald in den Lungen, Gehirn, und anderen Organen auftritt, ganz wie wir es bei der Anlage zur Arteriosklerose beobachten, wo bald Gehirnapoplexie, bald Angina pectoris, bald Endarteritis obliterans, die Todesursache bildet.

Wir müssen bei der Frage über Phthise nicht vergessen, dass es auch nicht- tuberkulöse Phthisiker giebt, z. B. bronchiektatische oder katarrhalische Phthise alter Leute, karzinomatöse aktinomyköse Phthise, und besonders auch chronische indurative Lungenentzündungen nach Staubinhalationen, die tuberkulös werden können, aber nicht müssen.

Bei der Ubiquität der Tuberkelbazillen entsteht nur dann Phthise, wenn die infizierten Organismen dazu die Bedingungen, d. h. Anlage bieten. Und wie gross ist die Infektion der Lungen ohne nachfolgende Phthise! Nach Nägeli, Franz u. a. hat jeder Mensch nach dem 30. Jahre Reste von stattgefundener Infektion mit Tuberkelbazillen. Wer aber einmal die Disposition zur Schwindsucht ererbt, die ja qualitativ verschieden ist, so kann die Anlage auch ohne Tuberkelbazillen, allein durch Influenzabazillen oder durch Strepto- oder Staphylokokkeninvasion den Tod zur Folge haben, ist also im Grunde gestorben an den Folgen ererbter Anlage zur Phthisis.

Es steht ja fest die Ubiquität des Tuberkelbazillus, ich meine natürlich die Ubiquität nicht vom bakteriologischen, sondern epidemiologischen Standpunkte.

Auf Grund alles gesagten kommen wir zum Schluss, dass bei der Entstehung der Phthise der konstitutionelle Faktor die Hauptrolle spielt. Der Phthisiker, wie schon Hippokrates sagte, stammt ab vom Phthisiker. Es wird gewiss ein reichliches Material für Infektionen Gesunder produziert, aber diese Keime müssen erst unter geeigneten Bedingungen in die Lungen gelangen und infizieren, aber das ist noch keine Phthise, sondern kann erst zur Phthise werden, wenn die Tuberkelbazillen im Gewebe auswachsen können. Viele der eingedrungenen Mikroben befördern die Lungen hinaus oder vernichten sie oder hindern sie am Auswachsen. Die Widerstandsfähigkeit desselben Individuums ist ausserdem nicht zu allen Zeiten gleich und eine mässige kann durch eine grosse Zahl von Keimen überwunden werden. Diese Möglichkeit ist aber dort am grössten, wo die meisten Keime in die Aussenwelt gelangen, d. h. in der Nähe eines Phthisikers, und es ist menschlich ganz begreiflich, dass man den Kranken meidet und sich nicht

unnötiger Gefahr aussetzt. Nur darf dieses instinktive Schutzbestreben nicht bis zur Ausstossung der Kranken gehen. Wir wollen gegen die Tuberkulose und nicht gegen die Tuberkulösen kämpfen (Saugmann).

Bei richtiger Wahl des Personals, richtiger Wohnung und Ernährung, bei gründlicher hygienischer Schulung bietet die gesteigerte Infektion in Sanatorien, Kurorten, Hospitälern, und Privatwohnungen, sowie Haus-Sanatorien keine Gefahr. Wenn das für die am meisten Exponierten gilt, muss es für die weitere Bevölkerung erst recht gelten. Die einheimische Bevölkerung der Kurorte hat nirgends eine Zunahme an Tuberkulose erkennen lassen. Der richtig erzogene Phthisiker ist somit keine Gefahr für die Umgebung. Der Kampf gegen die Tuberkelbazillen ist aber, selbst wo sie in gehäufter Weise in Betracht kommen, doch im Grunde nur ein Kampf für Reinlichkeit und kann durch Erziehung zur Reinlichkeit erfolgreich geführt werden. Das belastete Individuum aber ist therapeutisch zu behandeln durch Stärkung des Organismus vermittelst hygienisch-diätetischer Massnahmen. Auf diesem Wege werden die aus gesunden, aber zuweilen recht schwachen Determinanten entstandenen Eigenschaften im Organismus gestärkt im Kampfe mit den aus pathologischen Determinanten hervorgegangenen, die ihrerseits auch qualitativ verschieden sind und somit der Kampf auf günstigen Erfolg natürlich in gewissen Grenzen zu erhoffen ist; zuweilen sind die Eigenschaften so stark entwickelt, dass keine Mittel helfen sie zu bekämpfen, und der Organismus muss erliegen.

Die Bazillen muss man vernichten, wo man ihrer habhaft werden kann, aber zu glauben, dieselben einmal ganz aus der Welt zu schaffen, ist ja eine Utopie. Stärkung des ganzen Organismus macht denselben fähig, den einen erfolgreichen Kampf mit Tuberkelbazillen durchzuführen und darauf muss unser *Hauptaugenmerk* gerichtet werden.

Bei der Schwindsucht spielt somit die vererbte Anlage, d. h. die vererbte Disposition—endogenes Moment—die prävalirende Rolle, gegen welche wir mit hygienisch-diätetischen Massregeln am schnellsten mit Erfolg zu Felde ziehen. Die vererbte Disposition zur Schwindsucht ist also kein Wort "pour masquer notre ignorance," sondern sie stellt einen Factor dar, mit dem man unbedingt rechnen muss. Hippokrates hatte bis zu einem gewissen Grade Recht, wenn er sagte: "Der Phthisiker stammt ab vom Phthisiker."

LITERATUR.

Weissmann: Das Keimplasma, 1892.
Weissmann: Vorlesungen über Descendenztheorie, 1904.
De Vries: Befruchtung und Bastardirung, 1903.
Boveri: Ergebnisse über die Konstitution der chrom. Substanz, 1904.
Fick: Vererbungsfragen, etc., Ergbn. der Anat., etc., von F. Merkel, Bd. xvi, 1906.
Petrunkewitsch: Gedanken über Vererbung, 1904.
Ziegler: Die Vererbungslehre in der Biologie, 1905.
Hertweg: Ergebnisse und Probleme der Zeugungs- und Vererbungslehre, 1905.

Heider: Vererbung und Chromosome, 1906.
Martius: Pathogenese innerer Krankheiten, 1906.
Martius: Krankheitsanlage und Vererbung, 1906.
Riffel: Die Erblichkeit der Schwindsucht, 1890 und 1902.
Unterberger: Zur Frage über die Erblichkeit der Schwindsucht, 1901.
Unterberger: Der konstit. Faktor in der Schwindsuchtsfrage, 1903.
Unterberger: Vererbung der Schwindsucht im Lichte biologischer Forschungen, 1907.
Schlüter: Die Anlage zur Tuberkulose, 1905.

Heredity in Consumption.—(Simon von Unterberger.)

1. The difference between the infectionists and the hereditarians as to the origin of consumption is relative rather than actual, depending upon emphasis laid on the organism, on the one hand, or on the carrier of infection, on the other. For the genesis of consumption, as of every other disease, a soil (the body) and an exciting cause (tubercle bacillus) are necessary.

2. The latest researches in embryology show us: first, that the chromosomes in male and female ovum-cells are of the same number; and, second, that they vary in quality.

3. Chromosomes and their manifold subdivisions correspond to the separate qualities of the fully developed organism. All chromosomes in the human species are inherited, either in manifest or in latent form; in this way we explain the phenomena of atavism.

4. All tendency to disease that appears in any individual is to be regarded as hereditary, whether or not the corresponding disease can be traced back each time to the parents or ancestors.

5. The tendency to consumption is inherited and may be developed by various agencies.

6. Numerous autopsies show that every man over thirty years of age has old remains of a tuberculous infection. These facts show how comparatively easily the human organism can overcome the tubercle bacilli, and give us the indication for our treatment: the strengthening of the organism by hygienic and dietetic means, the details of which have been worked out by the large sanatoria.

7. We must, of course, seek to destroy the tubercle bacillus as far as possible, but it is utopian to imagine that all the tubercle bacilli in the world can be annihilated. Our chief endeavors must therefore be directed toward strengthening the body.

ÜBER DIE ROLLE DER ERERBTEN DISPOSITION BEI DER ÄTIOLOGIE DER TUBERKULOSE.

Von Dr. Johann von Szabóky,
Budapest, Gleichenberg.

Nach einer Statistik, welche Verfasser an 1456 Tuberkulösen und an 1433 Nichttuberkulösen zusammen gestellt hatte, ergaben sich folgende Resultate:

1. Wir müssen die Infektionsgefahr anerkennen und jede prophylaktische Massregel mit Freude begrüssen, wir dürfen aber die Rolle der Infektion nicht überschätzen und durch übertriebene Verordnungen die so häufig vorkommende Phthisiophobie vergrössern.

2. Wir müssen die Wichtigkeit sowohl der ererbten als der erworbenen Disposition anerkennen; wenn die ererbte Disposition auch nicht zu häufig vorkommt, so oft aber, wie die erworbene, kommt sie, nach Verfasser, unbedingt vor.

3. Den grössten Prozentsatz zeigte die elterliche Belastung; zirka die Hälfte von diesem Prozentsatz fiel auf die väterliche, die Hälfte auf die mütterliche Seite; nur bei einem Drittel konnte man die Tuberkulose der Eltern schon vor der Geburt ihrer Kinder konstatieren. Einen kleineren Prozentsatz zeigte die grosselterliche, und den kleinsten die geschwisterliche Belastung.

4. Trotzdem der Habitus phthisicus hauptsächlich bei der ererbten, weniger bei der erworbenen Tuberkulose vorkommt, und nur selten bei nicht an Tuberkulose Erkrankten, kann man ihn weder für die Tuberkulose, noch für die ererbte Disposition als charakteristisches Symptom bezeichnen.

5. Die ererbte Disposition übte auf die Schwere der Fälle keinen Einfluss aus; Ausnahmen bildeten nur die Fälle, wo eine vielseitige Belastung vorhanden war; diese nahmen auch einen schwierigen Verlauf.

6. Die erbliche Belastung kam im Verhältnis bei älteren Menschen fast ebenso oft vor wie bei den jungen Patienten.

7. Das Brehmer'sche Gesetz konnte Verfasser nur selten bestätigen.

Hereditary Disposition as a Factor in the Etiology of Tuberculosis. —(VON SZABÓKY.)

The author announces the following results of statistics which he collected from 1456 tuberculous and from 1433 non-tuberculous cases:

1. The danger of infection should be recognized and every prophylactic measure hailed with joy, but the danger of infection should not be overestimated nor should the oft-recurring phthisiophobia be magnified by excessive precautions.

2. The importance of hereditary as well as acquired disposition must be recognized; for although hereditary disposition is not too frequently, it is, nevertheless, according to the author, quite as frequent as acquired disposition.

3. The greatest rate of percentage was shown by those with an inherited taint, about one-half on the father's and one-half on the mother's side. In only one-third of the cases tuberculosis showed itself in the parents before the birth of their children. A smaller percentage showed tuberculosis in the grandparents and in the smallest percentage of the cases tuberculosis in brothers or sisters was noted.

4. The phthisical habit cannot be designated as a characteristic of tuberculosis nor of hereditary disposition, although it occurs chiefly in hereditary cases, less often in acquired ones, and almost never in non-tuberculous individuals.

5. Hereditary disposition exerted no influence upon the gravity of the cases, except where the taint was inherited from various collateral relatives when the disease ran a severe course.

6. The inherited taint occurred relatively as often in older as in younger patients.

7. The author was very rarely able to verify the Brehmer law.

La disposition héréditaire dans l'étiologie de la tuberculose.— (VON SZABÓKY.)

L'auteur rapporte les résultats suivants, tires des statistiques faites dans 1456 cas de tuberculose et 1433 cas non-tuberculeux.

1. Il faut reconnaître le danger de l'infection et saluer avec joie toute mesure prophylactique; mais on ne doit pas exagérer le danger de l'infection, ni prendre des précautions excessives, qui ne peuvent qu' augmenter la phthisiophobie qui est déja trop répandue.

2. Il faut reconnaître l'importance des dispositions héréditaire acquire. Car, bien que la disposition héréditaire ne soit pas très fréquente, elle est, d'après l'auteur, à peu près aussi fréquente que la disposition acquire.

3. Le plus grand pourcentage de malades s'est montré chez les personnes qui ont hérité la disposition; environ la moitié de ce pourcentage a hérité la disposition du côté du père et la moitié du côté de la mère. Dans un tiers des cas seulement, la tuberculose s'est montrée chez les parents avant la naissance de leurs enfants. Dans un pourcentage plus petit, on trouva la tuberculose chez les grands-parents et la tuberculose chez les frères et les soeurs se trouva dans un nombre de malades représentant le plus petit pourcentage.

4. L'habitus tuberculeux ne peut pas être désigné comme caractéristique pour la disposition héréditaire, quoiqu 'il s'observe principalement dans les cas héréditaires, moins souvent dans les cas acquis et presque jamais chez les individus non-tuberculeux.

5. La disposition héréditaire n'exerce aucune influence sur la gravité de la maladie, excepté les cas où la disposition est héritée de différents parents collatéraux; dans ces derniers cas, la maladie est plus sévère.

6. La disposition héritée s'est trouvée aussi souvent, relativement, chez les vieux que chez les jeunes malades.

7. L'auteur n'a eu que très rarement l'occasion de vérifier la loi de Brehmer.

THE PRESENT STATE OF OUR KNOWLEDGE CONCERNING HEREDITY IN TUBERCULOSIS.

By Aldred Scott Warthin, Ph.D., M.D.,
Ann Arbor, Michigan.

This article, having come to hand late, is printed at the end of the proceedings of Section I (p. 377).—[Editor.]

LUNGENTUBERCULOSE UND ASTHENIA UNIVERSALIS.

Von Prof. B. Stiller,
Budapest.

Im Verlaufe meiner langjährigen Studien über die Enteroptose bin ich zur Aufdeckung einer constitutionellen Krankheit gelangt, welche die verbreitetste unter allen auf hereditärer Anlage beruhenden Krankheiten ist, der Asthenia universalis. Die Anlage gibt sich schon beim Kinde durch den atonischen Habitus kund: Zartes Skelett, langer, flacher Thorax, steil abfallende Rippen, breite Intercostalräume, enger Angulus epigastricus, und als Teilerscheinung des asthenischen Brustkorbes eine Lockerung des Rippenbogens in Form des Freibleibens der normaliter fixierten Spitze der 10. Rippe in Folge eines angeborenen Knorpeldefectes. Dieser Habitus hat die verschiedensten Grade von seiner höchsten Ausbildung bis zum Grad des normalen. Es gibt viele Fälle, wo der Habitus wenig markiert ist, dann genügt das Stigma der costa decima fluctuans zur Feststellung des asthenischen Habitus. Dieser aber ist nicht das Wesen der Anlage, sondern bloss der sichtbare Index der allgemeinen asthenischen Constitution, welche mit Atonie aller Gewebe, mit Hypoplasie des Herzens und der Gefässe, und anderen angeborenen Anomalien einhergeht.

Dieser Habitus und diese Constitution disponieren zu einer Reihe von Symptomen, welche sich meist erst nach der Pubertät entwickeln und zusammen die asthenische Krankheit ausmachen: Enteroptose, nervöse Dyspepsie und Neurasthenie. Die Astheniker sind dabei fast immer mager, von schlaffer Muskulatur, und anämisch, und zeichnen sich dadurch aus, dass auf Grund der Asthenie des Bauchsympathicus schon geringe Veranlassungen schwere Ernährungsstörungen erzeugen. Überdies zeigen sie meist Hyperacidität und Magenatonie, deren klinisches Zeichen das Plätschern und deren morphologischer Ausdruck die Gastroptose ist; endlich habituelle Obstipation als Folge der Darmatonie.

Meine eingehenden Untersuchungen an Phthisikern haben nun ergeben, dass nicht nur der asthenische Habitus mit dem phthisischen identisch ist, sondern dass der letztere eigentlich und nach seiner ursprünglichen Bedeutung der asthenische ist, und ebenfalls fast stets das Stigma costale aufweist. Dieser Körperbau ist seinem Wesen nach nur der Index der asthenischen Constitution und bedeutet erst secundär die Anlage zur Phthise; mit anderen

Worten: die Asthenie involviert die Disposition zur Phthise. Demgemäss finden wir bei allen durch den Habitus gekennzeichneten Lungenkranken auch meist Enteroptose, nervöse Dyspepsie, und Neurasthenie, sowie alle übrigen funktionellen Störungen des Morbus asthenicus. Auch der psychische Habitus ist derselbe; beide zeigen häufig einen lebhaften Geist, oft bedeutendes receptives, seltener schöpferisches Talent, noch seltener starke Willensenergie, dafür Einbildungskraft und Impressibilität. Wir finden unter den Asthenikern und Phthisikern oft Künstler und Dichter, während wirklich beschränkte, dumme, stumpfsinnige Menschen unter ihnen nur selten angetroffen werden.

Die bei Phthisikern in 70–90% constatierte Dyspepsie ist nichts anderes als die der Asthenie legitim zugehörige nervöse oder enteroptotische Verdauungsstörung. Die sogenannte prätuberculöse Dyspepsie, der Gegenstand so vieler Controversen, ist durch die Beziehung der Phthise zur Asthenie vollkommen klar gestellt; denn sie ist nichts anderes als eine bei Asthenischen oft vorkommende schwere Dyspepsie und Ernährungsstörung, die den Ausbruch einer meist ebenfalls schweren Phthise begünstigt.

Die Annahme vieler Autoren von bedeutenden Namen, dass der phthisische Habitus nur durch die emaciirende Wirkung der Krankheit entsteht, und vor derselben gar nicht vorhanden sei, wird durch die Identifizierung desselben mit dem asthenischen ein für allemal über den Haufen geworfen. Denn wir begegnen demselben bei Tausenden von Asthenikern, und der Rippendefect, der enge epigastrische Winkel, und die ganze Conformation des Skeletts sind angeboren, und können als anatomische Anomalie gar nicht erworben werden.

Das Freund'sche Zeichen, die Verkürzung und Starrheit des 1. Rippenknorpels, wird neuestens als bedeutendster Factor beim Zustandekommen der Lungentuberculose hingestellt, indem es die gehörige Lüftung der Lungenspitzen beeinträchtigt. Dies ist eine grosse Übertreibung. Diese angeborene Anomalie ist nur ein häufig vorkommendes Attribut des asthenischen Habitus, und wirkt bloss mit dazu bei, dass die Spitzen leichter erkranken. Aber die grosse allgemeine Disposition, welche in der ganzen Constitution liegt und sich im ganzen Habitus ausdrückt, ausschliesslich in jener geringen Anomalie suchen zu wollen, ist ein Verkennen des wirklichen pathologischen Geschehens. Und wenn man auf Grund jener einseitigen mechanischen Auffassung mittelst Durchschneidung des verkürzten Knorpels die Phthise verhüten oder heilen will, so ist dies eine therapeutische Chimäre. Als wenn man dadurch den ganzen asthenischen Organismus mit seiner allgemeinen Atonie, seinen zahlreichen secretorischen, motorischen, und nervösen Störungen, welche insgesammt eben die Veranlassung zur Phthise bilden, auch nur im geringsten beeinflussen könnte.

Die asthenische Constitution ist aber nicht bloss der Nährboden für

die Phthise, sondern auch für andere Krankheiten, so für die Chlorose, für das Magengeschwür, für die asthenische Albuminurie; während sie gegenüber anderen Affectionen einen gewissen Antagonismus zeigt, so gegenüber der Fettsucht, Gicht, chronischem Rheumatismus, degenerativen Herz- und Gefässkrankheiten, welche zu dem entgegengesetzten, nämlich dem apoplectischen Habitus, in genetischer Beziehung stehen.

Endlich sei bemerkt, dass die moderne hygienisch-diätetische Prophylaxe und Behandlung der Lungentuberculose nicht eigentlich die Therapie der Phthise, sondern die der Asthenie ist, und ihre richtige theoretische Begründung darin findet, dass sie eine eminent causale, d. h. eine gegen die constitutionelle Grundlage der Phthise gerichtete Therapie der Phthise ist.

Tuberculosis of the Lungs and Asthenia Universalis.—(STILLER.)

1. Asthenia universalis is a wide-spread constitutional disease, in the sense that it depends on hereditary tendency. Its attributes are: enteroptosis, nervous dyspepsia, severe disturbance of nutrition without sufficient cause, atony of the stomach with flatulence, intestinal atony, neurasthenia, and flaccidity of all tissues.

2. The tendency shows itself in the atonic habit of the child; delicate skeleton; long, flat thorax; oblique ribs; small epigastric angle; and, as a concomitant of the asthenic thorax, looseness of the costal girdle due to congenital defect of the tenth costal cartilage, which produces a floating tenth rib (normally fixed).

3. The phthisical habit is nothing else but the asthenic; this is its original meaning; that is to say, the asthenic habit is the index of the hereditary, asthenic constitution, which also predisposes to phthisis. In nearly all consumptives who present the phthisical habit we find a floating tenth rib, and, in a greater or less degree, enteroptosis, nervous dyspepsia, neurasthenia, and all the other above-mentioned attributes of asthenia.

4. In 70 to 90 per cent. of consumptives, dyspepsia is nothing but enteroptosis or nervous dyspepsia. So-called pretuberculous dyspepsia is a severe form of nervous dyspepsia, in which tuberculosis is superadded to a severe nutritional disturbance.

5. Freund's sign is only a concomitant of the asthenic habit. The shortening and stiffening of the first costal cartilage doubtless increase the predisposition of the apices, but its etiologic significance has been greatly overestimated as compared with the whole asthenic constitution, which represents the real predisposition. Division of the shortened

cartilage for prophylactic or curative purposes is therefore a therapeutic error.

6. The opinion of many authorities that the phthisical habit is only a product of the disease is based on the doctrine of asthenia. There are many asthenic persons who have the habit without being phthisical, and the individual anatomical anomalies of the phthisical habit can only be regarded as congenital.

7. The modern hygienic and dietetic treatment of tuberculosis in its true sense is a direct treatment of asthenia and not really of pulmonary tuberculosis.

Before adjourning the Section, the President, Dr. Welch, announced that the Section would next meet in joint session with Section II at 9.30, on Tuesday morning, in the Assembly Hall, to discuss

THE OPSONIC INDEX; THE CONJUNCTIVAL AND CUTANEOUS REACTIONS: SERUM DIAGNOSIS.

(See page 387.)

SECTION I.

Pathology and Bacteriology (*Continued*).

THIRD DAY. MORNING SESSION.

Wednesday, September 30, 1908.

INFECTION OF THE SKIN. SOURCES OF INFECTION.

The Section was called to order by the President, Dr. Welch, at half-past nine o'clock.

INOCULATION TRANSCUTANÉE DE LA TUBERCULOSE.

PAR MM. LES DOCTEURS J. COURMONT ET LESIEUR,

Lyon.

De tres nombreuse expériences, nous concluions:

(A) *Les Faits:* 1. Qu'il s'agisse du cobaye, du veau ou du lapin, la peau, en apparence intacte, ou rasée, ou épilée, laisse facilement pénétrer le bacille tuberculeux, dans certaines conditions.

2. Les principales conditions sont les suivantes: le bacille doit être suffisamment virulent; il ne doit pas être englobé dans les crachats, des matières fécales ou des lésions. Cependant la réussite est possible même dans ces cas, surtout avec les crachats.

3. Si l'inoculation est positive, la peau se comporte de 3 façons différentes. Dans un tiers des cas, environ, elle ne conserve aucune trace du passage des bacilles; elle n'a pas été lésée. Dans un autres tiers, elle présente seulement un peu d'induration, ou des croûtelles en apparence banales; ces lésions sont cependant histologiquement tuberculeuses. Enfin, dans l'autre tiers des cas, on observe des tubercules verruqueux, d'ailleurs toujours petits et discrets.

4. Chez le cobaye et le veau, les ganglions de voisinage deviennent

tuberculeux, même sans lésion cutanée; chez le lapin, le système lymphatique reste indemne, qu'il y ait ou non lésion cutanée. Cela était à prévoir.

5. La généralisation se produit le plus souvent chez le lapin et le cobaye, si le bacille est suffisamment virulent. Elle est, en tous cas, toujours beaucoup plus lente que par l'inoculation sous-cutanée.

6. Chez le lapin, les lésions locales ou de généralisation ont une tendance marquée à la cicatrisation.

7. Chez le cobaye, inoculé sur la face interne de la cuisse, les ganglions inquinaux sont plus atteints que les cruraux; ils deviennent énormes et s'abcèdent très souvent; c'est là une légère différence avec la tuberculose par inoculation sous-cutanée. En outre, les ganglions du côté opposé se prennent plus vite et plus souvent que par cette dernière' Les lésions ganglionnaires ne sont pas absolument superposables dans l'inoculation sous-cutanée et l'inoculation transcutanée.

(B) *Réflexions:* 1. La peau, même en apparence intacte, est loin d'être (grâce probablement aux poils) une barrière infranchissable au bacille tuberculeux. Cette porte d'entrée ne doit donc pas être négligée dans la pratique humaine ou vétérinaire. Beaucoup de tuberculoses peuvent provenir d'une inoculation transcutanée (rasage, épilage, lésion minime, etc.). La prophylaxie doit mettre ces notions à profit.

2. Les bacilles pouvant passer sans laisser de traces cutanées, l'absence d'une lésion cutanée n'est pas un argument à opposer à cette voie d'introduction.

3. On voit, combien variable et inattendue peut être l'origine des tuberculoses viscérales et notamment pulmonaires. Outre l'origine pulmonaire et intestinale, il y a l'origine muqueuse et cutanée. Le lapin, offrant une tuberculose pulmonaire, d'origine transcutanée, sans lésions ni cutanées ni lymphatiques, est un exemple de phtisie d'origine bien éloignée des voies respiratoires et de porte d'entrée impossible à découvrir. C'est la notion la plus importante à retirer de nos expériences.

4. L'inoculation transcutanée permet de produire expérimentalement soit la tuberculose verruqueuse cutanée, soit les lésions scrofulo-tuberculeuses de l'homme (inoculation avec des bacilles peu virulents, n'entraînant pas de généralisation).

5. Cette méthode ne peut être substituée à l'inoculation sous-cutanée ou péritonéale soit pour le diagnostic de la tuberculose, soit pour l'inoculation d'organes en séries.

Transcutaneous Inoculation of Tuberculosis.—(J. COURMONT AND LESIEUR.)

From a large number of experiments we draw the following conclusions:

(A) *The Facts:* 1. In the case of the guinea-pig, the calf, and the rabbit the skin, although apparently intact or deprived of the hair, readily allows the tubercle bacillus to pass through under certain conditions.

2. The principal conditions are the following: The bacillus must be sufficiently virulent; it must not be inclosed in sputum, in fecal matter, or in (tuberculous) lesions; but even under these conditions the experiment may be successful, especially with sputum containing bacilli.

3. If inoculation is positive, the skin reacts in one of three ways: In about one-third of the cases it shows no trace whatever of the passage of the bacilli—the skin has not been injured; in another third it presents merely a little induration or insignificant scabs; these lesions, however, are histologically tuberculous. Finally, in another third of the cases, warty tubercles, although very small and discrete, are observed.

4. In the case of the guinea-pig and the calf the neighboring glands become tuberculous even in the absence of any cutaneous lesion. In the rabbit the lymphatic system escapes, whether there be a cutaneous lesion or not. This might have been foreseen.

5. General tuberculosis develops most frequently in the rabbit and in the guinea-pig if the bacilli are sufficiently virulent; but in any event it is much slower than after subcutaneous inoculation.

6. In the rabbit the local, as well as the general lesions show a marked tendency to cicatrization.

7. In the guinea-pig, when inoculated on the inner aspect of the thigh, the inguinal glands are more severely involved than the crural glands; they become enormous and very frequently suppurate. This constitutes a slight difference from what is observed in tuberculosis following subcutaneous inoculation. In addition, the glands on the opposite side become involved more quickly and more often than after subcutaneous inoculation. The glandular lesions from subcutaneous tuberculosis do not coincide accurately with the lesions observed in the transcutaneous form.

(B) *Observations:* 1. The skin itself, although apparently intact, is far from offering an impassable barrier to the passage of the tubercle bacillus. (This is probably due to the hair.) Hence this portal of entry must not be neglected in medical and veterinary practice. Many tuberculous infections may result from a transcutaneous inoculation (abrasions, epilations, minute lesions, etc.). This principle should be utilized in prophylaxis.

2. Since the bacilli are capable of passing through the skin without leaving any trace, the absence of a cutaneous lesion is no argument against this mode of invasion.

3. These observations furnish additional proof how variable and unexpected may be the origin of visceral, especially pulmonary tuberculosis. In addition to the pulmonary and the more frequent intestinal origin, there is a possibility of entrance through mucous membranes and skin. A rabbit presenting pulmonary tuberculosis of transcutaneous origin, without either cutaneous or lymphatic lesions, furnishes an example of tuberculosis originating at a point far removed from the respiratory tract through a port of entry which it is impossible to discover. This is the most important deduction from our experiments.

4. By means of transcutaneous inoculation one can produce experimentally in man either warty cutaneous tuberculosis or the human scrofulotuberculous lesions (inoculation with bacilli of low virulence without general infection).

5. This method cannot be substituted for subcutaneous or peritoneal inoculation, either for purposes of diagnosis or for inoculating organs in series.

Inoculación Transcutanea de la Tuberculosis.—(J. COURMONT Y LESIEUR.)

Los resultados de un gran número de experimentos dan base á las conclusiones siguientes:

(A) *Los Hechos:* 1. En los cobayos terneros y conejos la piel aunque aparentemente intacta ó desprovista de pelos permite la entrada del bacilo de la tuberculosis bajo ciertas condiciones.

2. Las condiciones principales son las siguientes:—El bacilo debe ser suficientemente virulento; este debe estar contenido en el esputo en sustancias excrementisias ó en lesiones tuberculosas; aun bajo estas condiciones el experimento puede ser con éxito, especialmente con esputo que contiene el bacilo de la tuberculosis.

3. Si la inoculación es positiva la piel reactua en una de las tres maneras siguientes: Como en una tercera parte de los casos la piel no es afectada y el punto de entrada del bacilo es invisible; en otra tercera parte de los casos ésta presenta solamente un pequeño endurecimiento y una cicatriz insignificante; estas lesiones, sinembargo, son de caracter tuberculoso. Finalmente en la otra tercera parte se observan verrugas de caracter tuberculoso, aunque muy pequeñas.

4. En los cobayos y terneros, tuberculosis se observa en las glandulas vecinas aun en la ausencia de las lesiones cutaneas. En los conejos, como

era de esperarse, sin relación á la ausencia ó presencia de lesiones cutáneas, el sistema linfático no es afectado.

5. La tuberculosis general se desarrolla con mas frecuencia en los conejos y cobayos cuando el bacilo es suficientemente virulento, mas esta es mas lenta que en las inoculaciones subcutaneas.

6. En el conejo, en las lesiones locales y generales, se nota una tendencia marcada á la formación de cicatrices.

7. En el cobayo, cuando la inoculación es hecha en la parte interna de la pierna, las glándulas inguinales son mas severamente afectadas que las glándulas crurales, estas se agran lan enormemente y con frecuencia terminan en supuración. Esto constituye una diferencia de lo que se observa en las inoculaciones subcutaneas. Ademas las glandulas del lado opuesto son afectadas con mayor rapidez frecuencia que en las inoculaciones subcutáneas. Las lesiones glandulares en la tuberculosis subcutánea no coinciden exactamente con las lesiones observadas en la formas transcutáneas.

(B) *Observaciones;* 1. La piel misma auque aparentemente intacta, es incapaz de actuar como una barrera impenetrable á la entrada del bacilo de la tuberculosis. (Esto es debido probablemente á los pelos), por lo tanto esta puerta de entrada no debe menospreciarse en la Medicina y en la Veterinaria. Muchas infeciones de tuberculosis pueden resultar á consecuencia de la inoculación transcutanea (raspaduras descuamación, lesiones minutas, etc.). Este principio debe utilizarse en la profiláxis.

2. Puesto que el bacilo es capaz de penetrar la piel sin dejar señas del punto de entrada, la ausencia de las lesiones cutaneas no es un argumento en contra este modo de invasión.

3. Estas observaciones demuestran cuan variable é inesperado puede ser el origen de la tuberculosis pulmonar y de los intestinos. Además del origen pulmonar y el de los intestinos, también existe la posibilidad de entrada por medio de la piel y las membranas mucosas. El coneja, el cual presenta la tuberculosis pulmonar de origen transcutaneo, sin lesiones cutaneas ó linfáticas, pude tomarse como ejemplo del origen remoto de la tuberculosis pulmonar por medio de una puerta de entrada dificil de descubrir. Esta es la mas importante deducción de nuestros experimentos.

4. Por medio de las inoculaciones transcutaneas uno puede producir experimentalmente verrugas ó bien lesiones escrofulo-tuberculosas de la piel (inoculación del bacilo de poca virulencia incapaz de producir una infección general.)

5. Este método no puede substituirse por las inoculaciones subcutáneas ó peritoneales, bien con el objeto del diagnostico ó bien en la inoculación de los organos en series.

BEITRAG ZUR FRAGE DER PERCUTANEN INFEKTION.

Von Dr. Isidore Spitzstein,
Budapest.

Wir wissen, dass Prof. Krehl, Heidelberg, als er in seiner Pathophysiologie (1906) über die durch percutane Einreibung von Staphylococcen erzeugte Furunculose Garrés und die ebenfalls positiv ausgefallenen percutanen Infektionsversuche des österreichischen Pestkomitees bei Meerschweinchen referirt, das Gelingen der Ansteckung durch die scheinbar intakte Haut mit Wahrscheinlichkeit auf während der Einreibung entstandene kleine Verletzungen der Körperoberfläche und des Epithels der Hautdrüsen zurückführt. Ebenso hebt Prof. Cornet sehr hervor ("Die Tuberkulose," 1907), dass bei den cutanen Infektionsversuchen (Einreibungen mit Sputum, etc., an der Haut der Wangen, Nase, etc.), hatten je nachdem mehr oder minder oberflächliche Verletzungen vorausgegangen waren, eine Folge.

Die Untersuchungen C. Fränkels ("Über die Wirkung der Tuberkelbazillen von der unversehrten Haut aus," Hygien. Rundschau, 1907) lenkten die Aufmerksamkeit von neuem auf die Frage, indem es dem genannten Forscher gelang, bei Meerschweinchen bei unverletzter Haut allgemeine Tuberkulose auf percutanem Wege hervorzurufen.

Ich versuchte diesen Infectionsmodus auf Anregung meines Chefs, Dr. D. O. Kuthy, bei einer für Tuberculose wenige emfänglichen Tiergattung, bei dem Kaninchen, bei welchen nach den Angaben Cornet's in Folge von cutanen Infectionen auch der Tuberculosis verrucosa cutis ähnliche Veränderungen.

In dieser vorläufigen Mitteilung kann ich bis jetzt erst über das Resultat bei 9 Kaninchen Bericht erstatten.

Diese 9 Kaninchen wurden von mir mit der grössten Sorgfalt und Milde in dem modifizirten Verfahren, dass auch die kleinsten traumatischen Verletzungen an der Haut und an den Wandungen der in dessen Tiefe führenden Kanälchen (Haarbälge, Talgdrüsengänge) vermieden werden, mit Teilchen einer erprobt virulenten Reinkultur des humanen Tuberkelbazillus an der Bauchhaut 48-72 Stunden nach dem Abrasieren derselben eingerieben. Ein Tier ging nach 2½ Monaten ein, ohne dass Tuberkulose in demselben nachgewiesen werden konnte. Acht Tiere lebten gut fort, und von ihnen wurden 4 nach drei Monaten, 4 nach vier Monaten getötet. Lokale oder regio-

näre Veränderungen zeigten sich bei keinem derselben; in den inneren Organen konnte bei keinem Kaninchen die Tuberkulose nachgewiesen werden. Die bei Kaninchen gewissermassen prädisponirten Nieren und Lungen liessen ebenfalls keine Veränderungen wahrnehmen.

Aus meinem noch fortzusetzenden Versuchen muss ich demgemäss bisher folgern, dass wenn die wahre percutane Infektion überhaupt möglich ist, so bildet sie entschieden den ungünstigsten Infektionsweg für den Tuberkelbazillus, dessen Angriff von dieser Seite bereits durch die an und für sich noch bescheidene refractäre Eigenschaft des Kaninchens zurückgeschlagen wird.

The Question of Percutaneous Infection.—(SPITZSTEIN.)

Professor Krehl, Heidelberg, discussing the furuncles produced by Garré through percutaneous application of staphylococci and the positive percutaneous infection experiments with guinea-pigs of the Austrian Pest Committee in his Patho-physiology (1906), explains these successful infections through the apparently intact skin by considering it probable that the inunctions produced slight injuries of the surface of the body and of the epithelium of the skin-glands. Professor Cornet also emphasizes in his book ("Die Tuberculose," 1907) that the successful issue of the cutaneous infection experiments (sputum, etc., when rubbed into the skin of the cheeks, nose, etc.) depended entirely upon whether superficial injuries of greater or less extent preceded the infection.

The experiments of C. Fraenkel ("The Activity of Tubercle Bacilli Through the Intact Skin," Hygienische Rundschau, 1907) again called our attention to the question, inasmuch as this investigator produced general tuberculosis in guinea-pigs by treating them through the intact skin.

I performed my series of experiments with this mode of infection in the laboratory of the Königin Elizabeth Sanatorium; I employed a type of animal less susceptible for tuberculosis—the rabbit.

The skin of the abdomen of 9 rabbits was first carefully shaven; forty-eight to seventy-two hours afterward portions of a well-tested, virulent, pure culture of the human tubercle bacillus were rubbed into this area with the greatest care; the procedure was carried out with such gentleness that even the slightest traumatic injuries of the skin and of the walls of the canals going into its depth (the hair-follicles, sebaceous gland ducts) were avoided. One of the animals died after two and one-half months, but without development of tuberculosis. The other 8 animals continued to live; 4 were killed after three months and 4 after

four months. Neither local nor regional changes could be demonstrated in any of them, nor could tuberculosis be demonstrated in any of the internal organs. Neither did the kidneys nor lungs, which in rabbits are predisposed to the disease, to an extent show any changes.

My experiments, not by any means finished, support the following conclusion: If percutaneous infection is at all possible, it certainly is the most unfavorable mode of infection for the tubercle bacillus; in the case of the rabbit particularly so, as it is decidedly refractory to the disease.

SOURCES OF TUBERCLE BACILLI PRODUCING HUMAN TUBERCULOSIS.

By William H. Park, M.D.,
New York

Considered from the human standpoint, all are now agreed that the sources of tubercle bacilli to be seriously considered are the tuberculous tissues of men and cattle. For one or another reason all other sources are of little or no importance. The occasional occurrence, for instance, of tubercle bacilli in the flesh of sheep and hogs is of little danger, since such food is cooked before eating and is given rarely to the very young, who are the most liable to infection.

In the transmission of tubercle bacilli from man to man sputum is by far the most important factor. The infected feces are also worthy of consideration. Milk is practically the only means by which bovine bacilli reach man, but it may be infected primarily in the udder, or secondarily by the dropping into it of particles of feces or saliva containing the tubercle bacilli.

While all will agree to the above statements, the relative importance of the two types of bacilli and the exact conditions under which they are transmitted to man, and the paths by which they gain entrance, are still disputed and under investigation.

The Number of Living Bacilli in Sputum.—The expectorated sputum contains, as is well known, an enormous number of bacilli. These, contrary to some earlier opinions, have been shown by culture experiments on Hesse's medium and in animal tests to be mostly alive. A few months ago, for example, I mixed a day's expectoration of ten consumptives, and found that the injection of 0.00002 c.c. in guinea-pigs regularly produced tuberculosis.

The Presence of Bacilli in the Mucus in Cases of Tuberculosis.—Between periods of expectoration, there has been some difference of opinion as to the number of bacilli in the mouth mucus, and therefore as to the danger of the droplets expelled in sneezing and shouting, and of the spit. Moeller found bacilli in the mucus of only 3 out of 20, and Cornet considers this an average condition. This, I am certain, is too low an estimate. I chose at random 15 adult males, who, while in good physical condition, had fairly advanced pulmonary tuberculosis, and expectorated rather frequently. Some minutes

after coughing mucus was gathered from each person. In 5 of the 15 specimens of mucus, bacilli were present, on the average, in a thin smear, in every tenth oil-immersion field, and in one they were even more abundant. In 4 others characteristic bacilli were found in a search of less than two minutes. In the remaining 5 they were missed in a search of similar length. In this investigation the number of bacilli in the mucus varied with the number of bacilli in the sputum and its character. The longer the period after expectoration, the less, as a rule, was the number of bacilli.

The Various Things which may be Directly Contaminated by Sputum.—Some of the expectorated sputum always remains on the lips. The mouth is wiped off with the handkerchief, and the hands are usually contaminated. We all remember Baldwin's striking experiment of finding living bacilli usually present on the hands of consumptives. The clothing, writing utensils, books, drinking and eating utensils may all be contaminated. Through direct contact in fondling and kissing, or the use of soiled utensils, tubercle bacilli may be passed to others.

Infection of the Surroundings and Air.—The expectoration delivered on the floor or street does not infect the air immediately, but that fine droplets of mucus, which are expelled in violent coughing and sneezing, may infect the air in the immediate neighborhood of the patient, has been shown by Flügge and others. There is little, if any, infection cast off in ordinary talking, and in the air some feet even from coughing patients no bacilli have been found. The bacilli expectorated on the floor, sidewalk, or elsewhere may be gathered up by young children crawling on it, or by flies and other insects.

Viability of Tubercle Bacilli in Dried Sputum.—The tubercle bacilli in sputum, being inclosed in mucus, make a fine, adherent mass, which is difficult to pulverize; so that they are not readily broken up in a fine enough powder to rise in the air and be inhaled. Even in the powdered form, rather exceptionally fast air-currents are required to carry it. Tubercle bacilli have been proved, by oft-repeated experiments, to live a considerable time, so that among the millions expectorated at any time a few usually remain alive for from two to six months, if protected from sunlight; and under unusual conditions, for even a longer time. A point to remember is that there is a fairly rapid destruction of bacilli going on from the moment the sputum is expectorated.

The amount of exposure to light and other conditions determine the time required for the complete death of all bacilli. This may be in a few hours or in a few months. In 1905 Dr. von Sholly carried out some experiments for me which are of interest in this connection. With fresh sputum, proved to contain a very large number of tubercle bacilli, a test was made to determine their viability when the sputum was dried in the dark and in diffuse daylight. Glass and gauze were the media inoculated with the sputum.

As controls, healthy guinea-pigs, each about 250 gm. in weight, were inoculated with the fresh sputum intraperitoneally, with 0.001 c.c., 0.0001 c.c., 0.00001 c.c. respectively. Successive batches of guinea-pigs of uniform medium size were then inoculated intraperitoneally with emulsions made from this sputum dried at room temperature, one series dried in diffuse light and one in the dark, for twenty-four hours, three days, nine days, sixteen days, thirty-four days, thirty-five days, sixty-two days, and sixty-six days respectively. As the time of drying became greater, the dose given the animals was progressively increased up through 0.01 c.c., 0.1 c.c., 0.5 c.c., and 1 c.c.

Of the original control animals, the ones receiving 0.0001 and 0.001 showed typical lesions and tubercle bacilli; the one having the smallest dose, viz., 0.00001 c.c., did not become infected. From the pigs inoculated after twenty-four hours' drying on glass with 0.01 c.c. dose, tubercle bacilli were recovered. Three pigs were inoculated with the sputum dried on gauze for three days in the dark. Two of these, receiving 0.01 c.c. and 0.001 c.c. respectively, showed tuberculous lesions at autopsy, which were confirmed by finding the bacilli. The pig receiving 0.0001 c.c. was negative.

Disinfection of Infected Rooms.—While disinfection of premises after the removal of cases of pulmonary tuberculosis is imperative, nevertheless I agree with those who believe that the number of persons who have become infected from such rooms is very small compared to those who trace their bacilli to contact with the living patient and in his surroundings. In the last report from the Phipps Institute, Dr. Flick reports only 4.8 per cent. that can be considered as probably having derived their disease from infected rooms. Even in these cases the mode of infection is very doubtful. In New York city we know of almost no cases. This may be due, in part, to the fact that renovation and cleansing of rooms vacated by consumptives have been enforced for some years.

Source of Infection in Individuals.—The various ways by which bacilli may be transmitted from the sick to the well are all concentrated in the home. Personal contact and infected surroundings there combine and persist. We find all investigations agree that the greatest single source of contagion is the living tuberculous person in the house. Thus, of the 3733 patients that have attended the Phipps Institute, 1946 attributed their infection to the preceding or immediate generation. Some recent figures by Holt are instructive. He investigated the home conditions of 67 infants suffering from tuberculosis. He found a large percentage cared for by parents or relatives suffering from tuberculosis.

One hundred children, comprising 30 suffering from tubercular bone, and 70 from gland infections, at St. Mary's Hospital in New York city, were investigated by Dr. Krumweide for me; 23 of which were found to come from

families where tuberculosis existed. Outside of the home, 15 per cent. associated closely with a tuberculous person in their work, and 7 per cent. in social relatives. Altogether, 44 of the 100 knew of close contact with tuberculous cases.

The Dissemination of Tubercle Bacilli by Persons before they Realize that they have Tuberculosis.—The great majority of cases of pulmonary tuberculosis occur among the poorer classes. They form the bulk of the people and are the most liable to infection. I made careful inquiry among 100 cases as to the care they exercised as to their expectoration before they were told they had consumption. Ninety-two of the 100 stated that they had had coughed and expectorated for a longer or shorter time before they knew their condition. Five stated that they had been careful, 87 said they had taken no precautions whatever. Most of these said they had expectorated anywhere that came handy. None of these had used a receptacle or handkerchief. The great majority also took no precautions as to their association with others. The statements that these men made, only last month, show the necessity of regulating the expectoration of the well, for otherwise the great majority of men, at least, will during the early stages of tuberculosis continue to infect their surroundings and imperil the health of their families and associates.

Tubercle Bacilli in Milk.—It is now established that tubercle bacilli, sometimes in great numbers, are passed with the milk in udder tuberculosis. Whether they pass through the udder in small numbers when other organs only are infected, is a doubtful question, and one of little importance, as it is never possible to state that a tuberculous cow has no udder tuberculosis. Personally I have not been able to infect guinea-pigs with milk from expected cows with healthy udders in over 100 tests. Some apparently positive results have probably been due to the fact, as emphasized by Schroeder, that cows swallow their sputum and pass it by the feces; so that milk carelessly obtained becomes contaminated.

In this country and Europe from 10 to 30 per cent. of the cattle are infected with at least a trace of tuberculosis. The most carefully guarded milk rarely contains any bacilli, but the great mass of market milk, cream, and fresh butter is liable to infection. From 5 to 20 per cent. of the market milk of the largest cities is infected. The recent tests of New York city milk, reported by Hess, show that it is badly infected, 15 per cent. of the samples of grocery milk having bacilli. All people who drink milk by the glass or use cream or milk upon cereals or use fresh butter probably swallow bovine tubercle bacilli many times every year. Except the breast-fed babies during the first year, this includes pretty nearly the whole population.

The Relation between Injected Milk and Human Tuberculosis.—For infants the statistics collected by Dr. Flick are very interesting. Of 1206

persons suffering from tuberculosis attending the Phipps Institute, 1103, or over 90 per cent., were breast-fed.

Last fall I was brought in contact with this experience. At Randall's Island there were more than one hundred children of from three to six years of age. In order to provide a pure milk, a special herd of cattle was kept for them. For some reason suspicion was aroused, and the cows were tested with tuberculin. Nineteen of the 28 cows reacted. These were autopsied. The lungs were involved in 17. In 6 of these both lungs were affected. The remaining 2 that reacted showed involvement of mediastinal glands. The udder in no case was involved. One sample of milk tested from each cow did not infect guinea-pigs nor the feces, and yet, if Schroeder is right, the milk must have at times been infected. These children, although many had been fed for a year upon the milk, showed no signs of tuberculosis. Only 15 per cent. reacted to the tuberculin test.

While it is apparently true that adults, and even children, usually escape infection after drinking a few bovine tubercle bacilli, nevertheless it is now absolutely established that quite a number of children have contracted fatal generalized tuberculosis from such bacilli. Our results in the research laboratory, to be reported in another section, agree with those obtained in other investigations. In adults we have found no bacilli of the bovine type. In children we have found a considerable percentage of glandular and generalized tuberculosis to be due to characteristic bovine bacilli.

LES MOUCHES COMME AGENTS DE DISSÉMINATION DU BACILLI DE KOCH.

PAR DR. CH. ANDRÉ,

Lyon.

La dissémination des microbes pathogènes par les mouches a été mise en lumière ces dernières années par les recherches de Yersin et de Nuttal sur la peste, de Santchenko, de Chantemesse et Borrel sur le choléra, d'Auché sur la dysenterie, etc. La rôle que jouent les mouches comme vecteurs du bacille de Koch a été en particulier étudié ces dernières années par Spillman et Hausalter,* Hoffmann,† Lord,‡ et plus récemment par R. M. Buchanan§ qui a verifié que les pattes de mouches ayant sójourné sur des crachats tuberculeux, peuvent donner la tuberculose au cobaye.

Nous avons fait quelques expériences pour essayer de nous rendre compte du danger pratique de dissémination du bacille tuberculeux par les mouches.‖

1. Tout d'abord nous nous sommes assurés que les mouches ne contiennent pas à l'état ordinaire de bacilles acidorésistants, restant colorés en rouge par la méthode de Ziehl-Häuser et pouvant en imposer pour des bacilles de Koch. Dans le laboratoire où nous faisons nos recherches nous avons capturé 15 mouches et examiné leur excreta: ils ne contenaient pas de bacilles acido-résistants.

2. Lorsqu'on nourrit les mouches avec des crachats infectants et à plus forte raison avec des cultures de bacilles de Koch on voit apparaître dans les excréments des mouches un grand nombre de bacilles.

En pratiquant des inclusions de mouches ainsi nourries de crachats on peut suivre le trajet effectué par les bacilles. Nous en avons vu dans la trompe des mouches et leur estomac mais en petit nombre; leur séjour doit y être très court. Au contraire l'intestin est rempli, parait dilaté par les crachats avalés. Sur une coupe mince on peut compter parfois plus de 20 bacilles. Dans les cas où la mouche a été nourrie non plus de crachats mais

* Spillman et Hausalter: "Dissém. du b. Tuberc. par les mouches," C. R. Acad. Sciences, 1887, vol. cv, p. 352.

† Hoffman: "Ueber die Verbreitung der Tuberculose durch unsere Stubenfliege," Aerzt. Ver. in König Sachsen, 1888, et Jahresbericht, 1888.

‡ Lord: Public. of the Massachusetts Gen. Hop., t. i, No. 2, fev. 1906, et Jour. Amer. Med. Assoc., 31 Mars, 1906.

§ Buchanan: "The Carriage of Infection by Flies," Lancet, 24 Juillet, 1907.

‖ Ch. André: Société médicale des hôpitaux de Lyon, 1906.

de culture l'àbondance des bacilles est telle que l'on voit la lumière intestinale obstruée par un bouchon rouge uniquement formé de bacilles de Koch.

Nous n'avons jamais vu de bacilles que dans la lumière du tube digestif. Sur des mouches ayant ingeré des chachats (ou des cultures) depuis 24,48 ou 72 heures, depuis 5 jours et 9 jours les bacilles se recontraient uniquement dans l'intestin jamais nous n'en avons vu dans les tubes de Malpighi qui aboutissent à l'intestin moyen, jamais non plus dans les oeufs. Les mouches ne sont pas envahies par les bacilles de Koch, elles se contentent de les véhiculer à travers leur tube digestif. Les bacilles traversent assez rapidement l'intestin de la mouche. Ils apparaissent dès les premières heures, déja très nombreux six heures après que les mouches ont été mises en contact avec les crachats, ils sont très nombreux encore 24 heures après qu'on a supprimé aux mouches cette nourriture. Après 30 heures ils deviennent rares mais on en trouve encore après 48 heures, et même dans une expérience après 5 jours. Dans l'une de nos expériences nous avons nourri des mouches avec des crachats infectants, nous leur avons fait subir un jeûne de 24 heures, puis nous les avons placé dans une cage neuve avec du lait, ce lait injecté au cobaye a determiné chez lui une tuberculose généralisée.

3. Les mouches sont capables d'absorber et de charrier non seulement les bacilles des crachats fraichement expectorés mais encore ceux contenus dans les poussières séches. Plaçons quelques mouches avec des poussières de crachats déssechés à 37° melés à du sucre en poudre, quelques heures après receuillons sur des lames porte-objets les excréments de ces mouches; nous y voyons de très nombreux bacilles de Koch. Ces bacilles proviennent bien de l'intestin de la mouche et n'ont pas été apporté par ses pattes et sa trompe; en effet ils sont très nombreux dans certaines déjections, absents dans quelques autres et on n'en voit jamais parmi les nombreux microbes déposés sur la lame de verre entre les taches rondes des "chiures de mouches."

4. Enfin nous avons pu vérifier que les mouches ne contiennent pas seulement les bacilles de Koch quand elles sont placées avec des crachats dans des conditions expérimentales, toujours anormales mais aussi dans des conditions naturelles. A l'hôpital de la Croix-Rousse nous avons receuilli des mouches volant dans les salles. Ces mouches broyées aseptiquement dans l'eau salée stérilisées et injectées aux cobayes ont tuberculisé ces animaux. Les mouches d'une salle d'hôpital où sont quelques tuberculeux contiennent donc des bacilles infectants. Ce sont des agents très actifs de dissémination de ces bacilles qu'elles puisent dans les crachats où elles viennent toujours nombreuses (et aussi sans doute dans les féces) et qu'elles déposent ensuite dans les aliments. Dans les salles d'hôpital on peut vraiment dire qu'elles font un va et vient incessant entre les crachoirs et les plats.

Conclusions.—Ces faits montrent qu'en ville les mouches peuvent non seulement infector les aliments de la famille d'un phtisique, mais aussi aller

contaminer ceux des ménages voisins. Les bacilles en effet sont encore nombreux dans les excreta des mouches 24 et 30 heures après l'ingestion des crachats. Dans cet espace de temps les mouches ont pu voyager d'un appartement à l'autre et déposer des microbes chez des voisins qui auraient pu se croire à l'abri de tout contage. Le lait, le beurre, les fruits, les plats sucrés, les viandes froides laissées sur une table de cuisine doivent être fréquemment souillés ainsi d'excréments de mouches contenant des bacilles.

On doit donc s'efforcer de détruire le plus possible de mouches, d'ailleurs convaincues ou soupçonnées à bon droit de véhiculer d'autres germes nocifs que ceux de la tuberculose. Contre les larves de mouches on conseille d'arroser les matières organiques en décomposition où elles se developpent avec l'huile de schiste, contre les mouches adultes on préconise les papiers "tue-mouches," les papiers buvards formolés (Parant, d'autun).

La destruction complète des mouches est malheureusement bien difficile; ce qu'il faut faire c'est lutter contre la dissémination des bacilles par la désinfection des crachats et des féces, c'est protéger avec les couvercles à grillage métallique les aliments qui pourraient être souillés de "chiures de mouches."

La Mosca Como un Agente en la Diseminacion de Bacilo de Koch.—(André.)

Las moscas son un agente activo en la diseminación del bacilo de Koch por su contacto constante con el esputo y excrementos, por una parte y las sustancias alimenticias, por otra, las que éllas ensucian con las patas y especialmente con el excremento.

Los experimentos del autor demuestran lo siguiente:

1. Las moscas capturadas al aire libre no contienen bacilos resistentes a la acción del acido, que pudieran tomarse por equivocación por el bacilo de Koch.

2. Moscas que han sido alimentadas con esputo evacuan una cantidad considerable de bacilos con los excrementos. El bacilo aparece des pues de seis horas en los excrementos y algunos pueden encontrarse despues de cinco dias. Estas moscas, por lo tanto, tienen subrado tiempo para transportar el bacilo á grandes distancias y contaminar los alimentos en las casas, aparentemente proegidos del contagio por el hecho de no vivir en ellas un tísico.

3. Los alimentos infectados por las moscas que se han alimentado de esputo, contienen el bacillo de Koch y producen la tuberculosis en los cobayos.

4. Las moscas absorben facilmente el bacilo contenido en el polvo seco.

5. Las moscas capturadas en los hospitales producen la tuberculosis en los cobayos.

Conclusiones practicas.—El esputo y los excrementos de pacientes tuber-

culosis deben ser desinfectados; las moscas deben ser destruidas en cuanto sea posible; los alimentos deben protejerse por medio de cubiertas hechas de alambre ó de telas.

Fliegen als Verbreiter der Koch'schen Bacillen.—(ANDRÉ.)

Folgendes ist das Resultat der Untersuchungen: Fliegen sind ein aktives Mittel zur Verbreitung der Koch'schen Bacillen, weil sie fortwährend hin und her wandern von angestecktem Sputum und Fäces auf Nahrungsmittel, besonders auf Fleisch, Früchte, Milch, etc., und besudeln dieselben durch Berührung mit ihren Füssen und besonders durch ihre Absonderungen.

Die experimentellen Untersuchungen des Verfassers haben folgendes gezeigt:

1. Fliegen, welche in frischer Luft gefangen werden, enthalten keine säurefesten Bacillen, die für Koch'sche Bacillen angesehen werden könnten.

2. Fliegen, die mit Sputum gefüttert werden, entleeren ziemliche Quantitäten von Bazillen in ihren Absonderungen. Man findet die Bazillen sechs Stunden nach Aufnahme des Sputums und manchmal sogar fünf Tage nachher. Diese Fliegen haben somit vollauf Zeit, die Bazillen auf weite Strecken zu transportiren, und Nahrungsmittel zu verunreinigen in Häusern, welche scheinbar vor Ansteckung geschützt sind, weil sie keine Schwindsüchtigen beherbergen.

3. Nahrungsmittel, welche besudelt wurden von Fliegen, die mit Sputum gefüttert waren, enthalten inficirte Bazillen und erzeugen Tuberkulose bei Meerschweinchen.

4. Fliegen nehmen leicht im trockenen Staub enthaltene Bazillen auf.

5. Fliegen, welche aufs Gerathewohl in einer Hospital-Abtheilung gefangen wurden, erzeugten Tuberkulose bei Meerschweinchen.

Praktische Folgerungen.—Sputum und Fäces von Tuberkulösen müssen desinficirt werden; Fliegen sollten so vollständig wie möglich ausgerottet werden; Nahrungsmittel sollten geschützt werden durch Bedeckungen aus Drahtnetz.

Flies as Agents in the Dissemination of Koch's Bacillus.—(ANDRÉ.)

Flies are active agents in the dissemination of Koch's bacillus because they are constantly going back and forth between contagious sputa and feces and food-stuffs, which they pollute by contact with their feet, and especially with their excretions.

The experimental researches of the author show the following:

1. Flies caught in the open air do not contain any acid-fast bacilli that could be mistaken for the bacillus of Koch.

2. Flies that have been fed on sputum evacuate considerable quantities of bacilli in their excretions. The bacilli appear six hours after ingestion of the sputum, and some may be found as long as five days later. These flies, therefore, have plenty of time to carry these bacilli to a great distance, and to contaminate food in houses apparently protected from contagion, because not inhabited by a consumptive.

3. Food polluted by flies that have fed on sputa contains infective bacilli and produces tuberculosis in the guinea-pigs.

4. Flies readily absorb bacilli contained in dry dust.

5. Flies caught at random in a hospital ward produce tuberculosis in the guinea-pig.

Practical Conclusions.—The sputa and feces of tuberculous subjects must be disinfected; flies should be destroyed as completely as possible; food-stuffs should be protected by means of covers made of wire gauze.

THE POSSIBILITIES OF INFECTION FROM TABLE UTENSILS AT SANATORIUMS.

By J. Woods Price, M.D.,
Saranac Lake, N. Y.

In the following experiments forks, spoons, tea-cups, and milk glasses in constant use at the Reception Hospital, Saranac Lake, were used. This institution receives patients suffering with pulmonary tuberculosis, a large majority of whom are in an advanced state of the disease, and some of whom are in the last stages.

The experiments were done without the previous knowledge of the nurses or maids of the institution, and several months apart, to avoid the possibility of the dishes receiving an extra good washing.

For the first experiment thirty forks and twenty-five each of spoons, cups, and tumblers were selected immediately after breakfast and after ordinary good washing, but not sterilization. The modus operandi of this experiment was as follows: The utensils were first thoroughly cleansed with a mop or cloth, with soap and water as hot as the maids' hands could stand, and then rinsed in running water as hot as it could be delivered through a pipe leading from a tank containing boiling, or almost boiling water, and then dried with a cloth.

In order to obtain the material for the experiment, the articles selected were, after the usual washing, well rubbed with a sterile 0.5 per cent. sodium bicarbonate solution, by means of sterile cotton swabs on glass rods, and these washings used for the inoculation of guinea-pigs. The washings were taken at once to the laboratory, and distributed among 56 guinea-pigs by subcutaneous injection into the right groin, 0.75 c.c. to each pig, and with the use of sterile syringes. The distribution was as follows:

Washings from forks, 14 pigs.
" " spoons, 14 pigs.
" " cups, 8 pigs.
" " tumblers, 8 pigs.
Mixed washings of cups and glasses, 6 pigs.
" " of forks and spoons, 6 pigs.

One animal died on the second day after the inoculation, and thirteen others from time to time up to the forty-first day, when all living animals

were killed. Each animal was autopsied at the time of its death or when killed, and all were found to be free of tuberculous infection. Smears were made on slides from the spleens and right inguinal glands of all those pigs killed on the forty-first day, and examined microscopically for tubercle bacilli, and found to be negative in every instance, nor could tubercle bacilli be demonstrated in stained specimens of the centrifugalized washings before inoculation.

In the second experiment five articles of each sort were selected immediately after use and before washing of any kind, and swabbed with the 0.5 per cent. sodium bicarbonate solution, as described above. These washings, which were very cloudy with particles of food, were, immediately upon arrival at the laboratory, injected into eight guinea-pigs, in the same manner as in the first experiment, the washings of each set of articles being divided between two pigs.

All these animals lived until the forty-first day, when they were killed and autopsied, and all, excepting the two inoculated with the washings from the milk glasses, were found to be tuberculous. It was an easy matter to demonstrate tubercle bacilli on slides made from the glands and spleens of these pigs, though no tubercle bacilli had been found in a casual search of smears made from the washings previous to inoculation.

The third experiment was a repetition of the first, but with the use of only six each of utensils and twelve pigs, the washings from the different articles being divided among three pigs. This was made eight months later, when the dish-washing was being done by a new set of maids, but under the supervision of the same corps of nurses. The result was the same.

It is fully realized that two experiments are not sufficient for definite conclusions, and that sterilization of eating utensils by heat or boiling, when possible, is not to be discouraged; at the same time, when the dish-washing is thorough, the danger of infection from this source does not seem to be very great.

My thanks are due to the Saranac Laboratory and the Reception Hospital for facilities placed at my disposal for the experiment, and to Dr. Baldwin, who suggested it.

Die Möglichkeit der Infektion durch Tischgeräte in Sanatorien.—(PRICE.)

Gabeln, Löffel, Teetassen und Milchgläser, die von vorgeschrittenen tuberkulösen Patienten fortwährend benutzt wurden, waren bei diesen Experimenten verwendet worden.

Am ersten Tage hatte man dreissig Gabeln, und von Löffeln, Trinkbechern und Teetassen je 25 ausgewählt, nachdem sie wie gewöhnlich gut gewaschen, aber nicht sterilisiert und mit einer sterilen 5% Sodalösung vermit-

tels steriler Wattebäuschen gereinigt worden waren, und die Auswaschung unter 56 Meerschweinchen durch subcutane Injection verteilt hatte. Von den vorgehabten Experimenten war den Hospitalwärterinnen oder Dienerinnen keine Kenntnis geworden. Alle Meerschweinchen wurden nach 41 Tagen getötet und als frei von tuberkulöser Infektion befunden.

Am zweiten Tage verschiedene Monate später wurden 5 Artikel von jeder Art sofort nach Gebrauch und bevor sie irgendwie gewaschen worden waren, in der oben beschriebenen Weise gereinigt und die Auswaschungen subcutan Meerschweinchen injiziert. Zwei Meerschweinchen auf alle fünf Artikel. Diese Tiere wurden ebenfalls einundvierzig Tage nach der Inoculation getötet und alle wurden tuberkulös befunden mit Ausnahme jener, die mit Auswaschungen von Milchgläsern injiziert worden waren und die keinerlei Verletzungen entwickelten.

Später wurde das erste Experiment unter Anwendung von sechs Artikeln verschiedener Art wiederholt und die Auswaschungen unter 12 Meerschweinchen mit demselben Resultate verteilt. Schmierpräparate, die von den Drüsen und Milzen aller in dem ersten und zweiten Experimente verwendeten Meerschweinchen gemacht und mikroskopisch auf Tuberkelbazillen untersucht wurden, ergaben in jeder Hinsicht ein negatives Resultat. Während die Sterilisierung der von Schwindsüchtigen verwendeten Tischgeräte nicht zu vernachlässigen ist, scheint dennoch die Infektionsgefahr von dieser Quelle, wenn es eben nicht möglich ist, nicht sehr gross zu sein.

BEITRAG ZUR FRAGE DER INFECTIONSGELEGENHEITEN.

Von Dr. S. Matejn,
Budapest.

Es wurden von mir auf Anregung meines Chefs, Herrn Docenten Dr. D. O. Kuthy, Tierversuche im Laboratorium des Königin Elisabeth-Sanatoriums mit Hilfe des Kollegen Miroszlav Lukits, angestellt, um zu erfahren, in welchem Masse die Tuberkelinfection durch verschiedene Factoren im alltäglichen Leben einer Lungenheilstätte auf den Gesunden übertragen werden könnte.

Dreizehn Meerschweinchen und 8 Kaninchen wurden teilweise mit dem Centrifugat einer Suspension von abgewaschenen, dann nach Trocknung fein zerriebenen Hausfliegen in sterilem Wasser subcutan geimpft; teilweise mit der Macerationsflüssigkeit (steriles Wasser) von den verosimiliter bespeichelten Teilen einiger Briefe, die von Aufnahme Suchenden stammten; teilweise mit der ebenfalls sterilen Abwaschflüssigkeit von Türklinken der Anstalt (gewonnen durch Ausdrücken von mit sterilem Wasser befeuchteten Wattebäuschen, mit welchen einige von Kranken stark benützte Klinken abgewischt worden sind), und endlich mit dem Abwaschwasser von Geldstücken, welche aus den Händen von Anstaltspatienten stammten.

Von den 21 Tieren hatte nur ein einziges Tier Tuberculose bekommen, ein Meerschweinchen, welches mit dem Centrifugat der Macerationsflüssigkeit von den Briefen dreier aufnahmesuchenden Kranken geimpft war.

Es scheint also, dass die Hülle und Fülle von Licht und Luft, sowie die mannigfachen Vorkehrungen des Heilstättenregimes zur Verhinderung der Uebertragung des Krankheitskeimes (das sorgfältige Sammeln des Auswurfes, das Vielreinigen, die stets bedeckten Spucknäpfe, etc.) ihr Ziel wahrhaftig erreichen.

Contribution to the Question of Opportunities for Infection.—(Matejn.)

At the instigation of my chief, Herr Docent Dr. D. O. Kuthy, I performed, with the assistance of my colleague, Miroszlav Lukits, a series of animal experiments in the laboratory of the Königin Elisabeth Sanatorium,

to determine to what degree the tuberculosis infection can be conveyed to the non-infected through the various factors in the every-day life of a tuberculosis sanatorium.

Thirteen guinea-pigs and eight rabbits were employed for the experiment. Some of them received subcutaneous inoculations of a suspension in sterile water of ordinary house-flies; the flies were first washed off, then dried and rubbed into a fine powder, then suspended in sterile water, which latter was finally centrifugated. Others were inoculated with the maceration fluid (sterile water) of parts of letters which had been moistened by the saliva of individuals who sought admission to the sanatorium. Still others were treated with the wash-water from doorknobs used by patients of the institution. The knobs were washed with cotton pads moistened with sterile water, the water being then squeezed from them. Other animals were treated with the wash-water from pieces of money handled by patients of the institution.

Of the twenty-one animals, only one developed tuberculosis; this was a guinea-pig, treated with the centrifugate of the maceration fluid coming from one of the letters of an individual seeking admission.

It seems, therefore, that the sum total of light and air, as well as the many special regulations to prevent the conveyance of the germ of infection (the careful collection of the sputum, the careful cleansing, the covered state of the cuspidors), in reality attained their purpose.

RELATIONS DE L'AIR AVEC LA TUBERCULOSE. STÉRILISATION DE L'AIR.

PAR MR. LE DR. SAMUEL BERNHEIM,

Paris.

De l'ensemble de son travail, l'auteur tire les conclusions suivantes:

1. Il y a une relation intime entre les microbes de l'air et la tuberculose. Plus l'atmosphère est chargée de bactéries, plus grand est le nombre de tuberculeux vivant dans ce milieu insalubre; tous les observateurs consciencieux ont consigné ces faits indéniables. On a donné à la tuberculose le nom de maladie de l'obscurité, parce que les microbes en général et le bacille de Koch en particulier se conservent très longtemp à l'abri de la lumière. Sous l'influence de la vie normale de nos habitudes, les microbes sont lancés dans l'air, l'homme les respire, ses poumons les retiennent, d'où infection et souvent contagion tuberculeuse.

2. L'absence ou au moins la rareté des cas de tuberculose dans certains climats (d'altitude ou de mer) sont encore des preuves des rapports étroits entre les microbes de l'air et la tuberculose. Cette dernière maladie est exceptionnelle dans ces climats où il y a une proportion infime de bactéries. À une certaine altitude on ne trouve même plus de germes dans l'air.

3. Pour des raisons analogues ou plutot inverses on a observé un nombre considérable de tuberculeux dans les grands centres où l'air est saturé de bactéries, dans les quartiers surpeuplés, dans les lieux de réunion, dans les hôpitaux, les prisons, les écoles, les casernes, les grands magasins, les administrations, les usines, les ateliers, etc.

4. Le meilleur moyen de combattre la tuberculose d'origine aérienne c'est de surveiller la salubrité des villes, l'hygiène des maisons où doit régner la propreté et où on doit faire pénétrer à profusion la lumière solaire. À ces moyens naturels on peut ajouter certaines mesures artificielles pour diminuer le danger des bactéries de l'air. En effet, on peut à l'aide de certains appareils de chauffage tels la cuve de M. le Dr. Goupil ou la cheminée à double courant de Mr. Silbermann détruire sur place tous les microbes contenus dans l'appartement. En d'autres termes, on parvient à assainir rapidement par cette méthode de chauffage naturel l'air le plus chargé de microorganismes. Ces cheminées sanitaires trouveront une application courante dans

tous les appartements et surtout dans les salles de médecine et de chirurgie, dans les amphitheâtres, dans les grandes salles où sont obligées de grandes collectivités et où l'agglomération augmente le danger de la contagion.

Relations of the Air with Tuberculosis: Sterilization of Air.—(BERNHEIM.)

1. The more the atmosphere is charged with bacilli, the greater the number of the tuberculous among those living under such atmospheric conditions. Tuberculosis is the disease of darkness because the bacillus of Koch lives long when protected from light.

2. The absence, or rarity, of tuberculosis in altitudes or at the sea-coast, demonstrates the relations of atmosphere to tuberculosis. The disease is unusual where the air carries few bacteria.

3. Wherever excessive numbers of bacteria are found in the air (as in overcrowded quarters, in assembly halls, factories, etc.) there tuberculosis becomes numerically important.

4. The best means of restricting tuberculosis (of aërial origin) is in the sanitary surveillance of cities, in domiciliary hygiene, and especially in the freest possible admission of sunlight. To natural means one should add such devices as those of Goupil and of Silbermann, by which the bacteria are destroyed in, or removed from, the air. Such apparatus should be included in the heating and ventilating systems of medical and surgical clinics, of assembly halls, and wherever people assemble in numbers within walls.

Before adjourning, the President, Dr. Welch, announced that the Section would meet at half-past two in the Assembly Hall, in Joint Session with Section VII, to discuss—

THE RELATIONS OF HUMAN AND BOVINE TUBERCULOSIS.

(See Vol. IV. Index.)

SECTION I.

Pathology and Bacteriology (*Continued*).

FOURTH DAY. MORNING SESSION.

Thursday, October 1, 1908.

IMMUNITY.

The Section was called to order by the President, Dr. William H. Welch, at half-past nine o'clock. Professor A. Calmette, of Lille, Honorary President of the Section, and Professor Robert Koch, Honorary President of the Congress, were on the platform.

THE PROBLEM OF IMMUNITY IN TUBERCULOSIS.

By Edward R. Baldwin, M.D.,

Saranac Lake, N. Y.

It is my purpose to take a brief retrospect of past achievements in attempts to artificially protect against tuberculosis, and then to indicate what seem to me the special problems for the future.

It must be confessed that much discouragement has resulted from the numerous experiments on animals in this direction during the past two decades. This problem has engaged the thought and labor of the foremost workers in immunity research, and it will continue to do so with the enthusiastic hope inspired by every new discovery, however little it may contribute to the ultimate object.

A review of the achievements already attained, with due credit to the authors for priority, is peculiarly difficult, and impossible in the limits of this address. The difficulties are real because of the simultaneous experimentation in different laboratories and countries which has independently followed similar lines, impelled by the same ideas. The most important example of this common *motif* is the principle of immunization with bacteria of attenuated virulence, formulated by the immortal Pasteur and applied to tuberculosis as soon as the illustrious Koch made it possible by

the discovery of the bacillus. It is noteworthy that this principle holds at present the leading place in the hope for success in the future, and it is natural that these experiments should have begun in France (Darenberg, Grancher, and Ledoux-Lebard, Martin, Hericourt and Richet, and Courmont and Dor). The immediate results were discouraging; too little was known of the mechanism of immunity to make use of the crude methods then employed as a basis for thorough experimentation; and the discovery of tuberculin and antitoxins for other diseases directed attention to these fields of greater promise.

As it is not generally known that Americans engaged in the earlier experimentation with a considerable degree of success, it is appropriate that they should receive mention here. As early as 1889 Dixon made some preliminary experiments with attenuated bacilli, and Trudeau, working under exceptionally difficult conditions, produced a relatively strong immunity with cultures of avian tubercle bacilli (1892), and later with attenuated human cultures. The late Emil de Schweinitz, in 1894, had more marked success on guinea-pigs immunized with the same attenuated cultures employed in Trudeau's experiments. This period was also one of diligent but unsuccessful search for antitoxic immunity by means of divers extracts and products of the tubercle bacillus. The soluble extracts of tubercle bacilli having failed to immunize animals, Koch introduced the emulsions or new tuberculins, "T. R." and "B. E.," which were in some degree protective against infection.

Experiments with pseudo-tubercle bacilli and mammalian types, supposedly altered by passage through reptilians, also promised fruitful results, but they have not fulfilled this hope up to the present time.

The discovery, by Theobald Smith, in 1895, of differences in form and virulence between bacilli from bovine and human sources was another valuable contribution, destined to influence the course of immunity experimentation on cattle. Pearson and Gilliland, in America, were among the first to attain a high degree of immunity in cattle by the use of the human type of bacilli, following up their first work by an extensive series of practical tests.

During the past decade many workers have turned to the study of immunity against tuberculosis in cattle. Von Behring and Koch, with their associates, have both introduced methods of immunization for cattle, the basis of which was the intravenous inoculation of living human cultures. The "Bovo-vaccin" of von Behring consisted of dried human cultures designed to be twice inoculated within an interval of three months. The "Tauruman" of Koch and Schütz was an emulsion of more virulent human type for a single protective inoculation. Coincidentally, Pearson and Gilliland succeeded equally well with successive inoculations during shorter intervals. Besides these methods, von Baumgarten employed subcutaneous inoculations with good results; Calmette and Guérin used the gastro-intes-

tinal route by feeding the protective virus; and Heymanns inclosed virulent bacilli in capsules which were introduced subcutaneously for immunization without resulting danger of infection. Klimmer, of Dresden, claims excellent results from the subcutaneous injection of avirulent and modified human bacilli supposed to be passed through lizards.

The world-wide interest created by von Behring's announcement, in 1902, of a practicable method of immunizing calves, led to the hope that this aspect of the problem had been solved. An enduring immunity for cattle, with no danger associated with it, was an alluring prospect, and extensive experiments were at once undertaken. The outcome of these has been less satisfactory than was hoped for. A high degree of resistance can be conferred by various methods of inoculation with human and attenuated bovine bacilli for a period varying from six months to two years. Unfortunately, exposure to natural infection or to inoculation with bovine virus after this period has resulted disastrously. Some of the animals completely lose their immunity and others retain but little of it. The situation is, therefore, at present not encouraging for the establishment of a long-continued immunity by any method, either in cattle or man.

Moreover, the use of living virulent bacilli as a bovine vaccine, either intravenously or subcutaneously, cannot be regarded as safe, since they have been discovered in the subcutaneous abscesses and milk at least nineteen months after the protective inoculation (Schroeder and Cotton and Weber and Titze). The trend of experimentation has naturally been toward the use of bacilli, either deprived of reproductive power, or modified by conditions of growth so as to lose parasitic features. The possibility of a strong relative immunity has been demonstrated, but much yet remains to be accomplished to make it useful.

To overcome the objections due to the use of living human bacilli in cattle, and to apply the principle of immunization to mankind, have been the problems of recent years. Hope of this achievement was held out by von Behring at the last International Congress at Paris in 1905. Nothing definite has been made public since to indicate that this hope was justified, or that the immunizing and therapeutic properties of the so-called "Tulase" were superior to the bacillary preparation, T. R. of Koch, introduced a decade before.

One fact has been prominent in the course of all investigations, and that is the superiority of living bacilli over all the preparations of dead bacilli for protective inoculation. The vital element has a more pronounced influence, even upon animals which completely resist infection by the immunizing vaccine and show no trace of the inoculated bacilli a short time afterward in their tissues. It is natural to suppose that the bacilli perish too quickly to adjust themselves to a parasitic existence by producing any hypothetical

secretion which might be the secret of their greater protective influence. It is admitted, however, that the degree of immunity is directly proportional to the virulence of the vaccine. The subtle difference between the immunizing value of living and dead bacilli needs more investigation, likewise also the cause of variations in virulence.

Repeated protective treatment must be considered necessary for success from the present outlook, and by means of an agent equally innocuous to cattle and mankind. It has been found that a period of two months after the first immunizing dose is required to develop the specific resistance in calves. Obviously, they must be protected from exposure to infection during this period. Probably the subsequent protective treatments will more quickly become effective.

It would appear desirable to establish as strong local resistance as possible by subjecting all avenues of infection to local immunization; for example, by feeding and inhalation of the vaccine.

In order to adjust the dosage and intervals, the finer mechanism of immunity must be closely studied. The agglutinin and opsonin tests have not been satisfactory measures of resistance, and some way of estimating specific latent antituberculous cell energy is needed. When natural infection is taking place or the individual is undergoing immunization, there are, it is true, evidences of changes in the blood, but when no such stimulus is active, the content of antibodies—agglutinin, opsonin, or lysin—slowly drops to a normal level. There is then no sign of the latent specificity, which we are as yet able to recognize, although a renewed infection or a tuberculin test may elicit it.

Another phase of the problem is to establish a correct balance between the specific response to infection which occurs during the hypersensitive stage of immunity, and the ability of the tissue-cells to assimilate the poisons without harm.

An immunity that tends only to arrest the infection, but not to overcome it, is not wholly beneficial when it creates ulceration at the portal of entrance of the bacillus (Th. Smith). Hence the question whether hypersensitiveness artificially induced by protective inoculations is beneficent or otherwise must be considered. It would seem vastly better, from what we know of the effects of hypersensitiveness in heightening the affinity of the body-cells to a harmful degree for the poisons of tubercle bacilli, that it should be avoided. Specific bacteriolytic powers are useful in combating bacteria, but not in assimilating the dead and digested body substances of bacteria.

Fortunately, the number of bacilli to be disposed of at any given time is small under natural conditions of infection. It is conceivable that a relative tuberculosis immunity, without tuberculin susceptibility being produced at some time during its development, might be defective. On the other

hand, complete tolerance to tuberculin in cattle may be associated with a high degree of resistance to infection.

The problem, therefore, seems to be to create tolerance for the bacillus poisons and its products which have resulted from lysis, or to aid their safe assimilation by the tissues.

Without the unknown quality called "tolerance," no real immunity can exist, and the earlier in life this can be established with absolute safety, the more resistant the adult must become. That there is danger of harm in the process may easily be surmised from the grave impairment of nutrition resulting from experiments with dead bacilli, and the well-known anemia accompanying so-called latent tuberculosis. These difficulties I conceive to be the prominent ones, but they are here treated in a confessedly superficial manner.

The studies of Bartel on the influence of lymphatic cells upon the tubercle bacillus, as well as those of Opie on the leukocytes, promise to enlarge our knowledge of this subject. Still more light may come from investigations now in progress on the mechanism of anaphylaxis and its prevention.

Finally, the problem of passive immunity is still a distant goal which should not be forgotten. It must not be thought hopeless, considering the progress of biological research, though a serum-therapy furnishes but a faint probability of success. Some other method of directly neutralizing the cell poisons may yet be discovered with the increasing facilities generously being devoted to medical research. On this rests the hope of an efficient therapy to supplement all other means of prevention and cure.

Das Problem der Immunität bei Tuberkulose.—(BALDWIN.)

Es ist ein Rückblick dessen gegeben, was in Versuchen, künstliche Immunität hervorzurufen, angestrebt worden ist, mit Erwähnung der noch ungelösten Probleme,—eine kurz gehaltene Revue, beginnend bei dem Anfange vorbeugender Inoculations-Experimente beinahe von der Zeit der Entdeckung des Bazillus durch Koch. Diese begannen naturgemäss in Frankreich mit der Anregung durch die brillanten Erfolge Pasteurs in der Anwendung verdünnter Bakterien. Es ist nicht allgemein bekannt, dass die Amerikaner unter jenen waren, die zuerst einen Grad von Erfolg erreichten, besonders Trudeau und de Schweinitz (1892–94).

Die Resultate waren im Ganzen entmutigend und man richtete die Aufmerksamkeit auf Versuche, antitoxische Immunität zu erzielen; während der Periode dieser wichtigen Entdeckung und der ersten Tuberkulinära, da die löslichen Extrakte von Tuberkelbazillen versagt hatten, Tiere zu immunisieren, führte Koch die Emulsionen oder Neutuberkuline T. R. und B. E. ein, welche teilweise Erfolg hatten.

Die Entdeckung der Virulenzunterschiede zwischen typischen Human- und Bovinbazillen durch Theobald Smith gaben einen Anstoss zu Forschungsarbeiten über protektive Inoculationen bei Rindern, während das Studium der verschiedenen Pseudo-Tuberkelbazillen und der durch die Passage durch Reptilien modifizierten die Hoffnung auf eine erfolgreiche Methode, künstliche Immunität hervorzurufen, erneuerten. Gleichzeitige Experimente, einen Schutz des Rindes durch den Humanbazillus hervorzurufen, wurden in verschiedenen Ländern gemacht, die alle einen bemerkenswerten Grad von Widerstandsfähigkeit der Inoculation gegenüber erreichten. Aber v. Behring kündigte zuerst ein "Bovo-Vaccin" an, von welchem er behauptete, dass es erfolgreich sei, wenn es in zwei aufeinander folgenden intravenösen Inoculationen angewendet wurde. Koch und Schütz folgten mit einer "Tauruman" genannten virulenteren Präparation. Der nächste deutliche Schritt war die Überwindung der Einwendungen gegen die Anwendung lebender Humanbazillen und des Immunisationsprinzipes menschlichen Wesen gegenüber. Es wurde von v. Behring auf die Hoffnung, dies erreichen zu können, beim letzten Kongresse in Paris 1905 hingewiesen. Seit damals war nichts Bestimmtes bekannt geworden, was diese Hoffnung hätte rechtfertigen können, oder dass die immunisierenden und therapeutischen Eigenschaften der sogenannten "Tulase" der zehn Jahre früher eingeführten bazillären Präparation T. R. von Koch überlegen waren. In der Zwischenzeit hatten andere Forscher mit ermutigendem Erfolge an Rindern gearbeitet durch Einteilung der Inoculationen in kürzere oder längere Intervalle (Pearson und Gilliland), mit Vaccinefütterung (Calmette und Guérin), mit Bazillen in Kapseln (Heymann), und mit jenen, die avirulent gemacht oder durch Passage durch andere Tierarten modifiziert worden waren (Klimmer). Das ist der heutige Stand der Forschung nach boviner Immunisierung. Die gegenwärtige Lage giebt keine Hoffnung für das Zustandekommen einer lange fortgesetzten Immunität durch eine Methode entweder beim Rinde oder beim Menschen. Die specifische Widerstandsfähigkeit der Rinder nach einer oder zwei Inoculationen mit Humanbazillen geht verloren und versagt vollständig nach sechs Monaten bis zu zwei Jahren. Des weiteren können lebende Humanbazillen in den Geweben zurückbleiben, oder in der Milch geschützter Kühe viele Monate nach der Inoculation ausgeschieden werden (Schroeder und Cotton; Weber und Titze).

Es wurde behauptet, dass subkutane Injektionen den Rindern einen ebensolchen Schutz angedeihen lassen, wie die intravenöse Methode, doch müsse die Gefahr einer lokalen Abszessbildung vermieden werden. Der feine Unterschied zwischen den Immunisierungswerten lebender und toter Bazillen verlangt eine Erforschung. Bis jetzt ist noch keine Methode der Inoculation lebender Bazillen gleichwertig erschienen. Man muss

vom gegenwärtigen Gesichtspunkte aus eine wiederholte Protektivbehandlung als notwendig erachten, die durch ein dem Rindvieh und dem Menschen gleichmässig unschädliches Mittel erreicht wird. Der Schutz gegen tuberkulöse Infektion muss also während einer Zeitperiode gesichert werden, die für die Entwickelung der speziellen Widerstandsfähigkeit nach der ersten Behandlung nötig ist, zum mindesten bei jungen Individuen.

Es erscheint auch erstrebenswert, dass alle Wege der Infektion auf lokale Immunisierung gerichtet sein sollten, wie zum Beispiel durch Einfütterung und Einatmung des protektiven Mittels. Der feinere Mechanismus der Immunität verlangt genaue Studien zur Bestimmung der Dosierung und Zwischenräume. Es ist eine Art von Immunitätsmessung nötig. Man muss ein genaues Gleichgewicht anstreben und erreichen zwischen der specifischen Antwort auf Infektion, welche während der überempfindlichen Phase der Immunität auftritt und der Fähigkeit der Gewebe, die Gifte ohne nachteilige Wirkung zu assimilieren. Eine Immunität, welche nur dahin strebt, die Infektion zu unterbrechen, aber nicht zu überwinden, ist nicht vollständig wertvoll, wenn sie Geschwürsbildung an den Eintrittspforten hervorruft. Daher muss die Frage in Erwägung gezogen werden, ob eine durch protektive Inoculation hervorgerufene künstliche Überempfindlichkeit von guter Wirkung oder etwas anderes ist. Es ist begreiflich, dass eine Immunität ohne Tuberkulin-Empfänglichkeit unvollständig sein mag; andererseits kann eine vollständige Toleranz für Tuberkulin mit einer hohen Widerstandsfähigkeit gegen eine Infektion bei Rindern vereinigt sein. Das Problem scheint zu sein, eine Toleranz zu schaffen für die Gifte des Bazillus oder dessen Produkte wenn sie gelöst werden, und ihre Assimilation durch die Gewebe.

Ohne das unbekannte "Toleranz" genannte Etwas kann keine wirkliche Immunität existieren, und je früher im Leben das mit absoluter Sicherheit erreicht werden kann, desto widerstandsfähiger muss der Erwachsene werden. Bartels Studien über den Einfluss der Lymphzellen auf den Tuberkelbazillus versprechen uns eine Erweiterung unserer Kenntnisse dieses Gegenstandes, ebenso als jene, die Opie über die Leukocyten gemacht hat.

Noch mehr Licht mag nun von Forschungen über den Fortschritt des Mechanismus der Anaphylaxe und seiner Verhinderung kommen. Schliesslich ist das Problem der passiven Immunität noch ein weit gestecktes Ziel, was nicht vergessen werden soll. Darauf beruht die Hoffnung auf eine wirkungsvolle Therapie.

SUR L'IMMUNISATION CONTRE LA TUBERCULOSE.

PAR MM. LES DOCTEURS A. CALMETTE ET C. GUÉRIN,
Institut Pasteur de Lille

Dans une série de travaux précédemment publiés* nous avons montré qu'on pouvait conférer aux animaux jeunes et adultes (boeufs, chèvres, cobayes) une résistance très-marquée à l'infection tuberculeuse artificielle par les voies digestives. Cette résistance s'obtient en faisant ingérer des émulsions fines de bacilles tuberculeux d'origine bovine, virulents ou modifiés par le chauffage à 70°. Chez les bovidés, une seule ingestion de bacilles virulents suffit en général à produire une infection assez légère pour qu'après avoir réagi à la tuberculine pendant 1, 2 ou 3 mois, ils cessent de réagir et deviennent capables de résister pendant plus d'une année à des ingestions massives ou répétées de doses de bacilles tuberculeux sûrement infectantes pour les témoins.

Les animaux vaccinés par cette méthode conservent dans leurs ganglions mésentériques pendant environ trois mois des bacilles vivants et virulents, capables d'infecter les cobayes auxquels on inocule le triturat de ces ganglions. Ils s'en débarrassent ensuite et, après 4 à 6 mois, on n'en retrouve plus.

Si l'on vient alors à les éprouver par inoculation intraveineuse, avec une forte dose de bacilles bovins virulents (5 milligr.), en même temps que les témoins de même âge, on constate que les témoins prennent toujours une tuberculose granulique à marche suraigüe, mortelle en 4 à 6 semaines, tandis que les vaccinés gardent pendant 8 mois au moins toutes les apparences d'une parfaite santé. Puis tout-à-coup, leur immunité disparaît: on s'en aperçoit parce que quelques-uns d'entre eux présentent brusquement des lésions tuberculeuses à localisations variables, et si l'on vient à sacrifier ceux qui n'en présentent pas encore, on trouve que leurs ganglions médiastinaux et bronchiques récèlent toujours des bacilles vivants et virulents pour le cobaye, alors même qu'il n'y existe aucune lésion tuberculeuse macroscopiquement visible.

Il est donc évident que les bacilles introduits par voie intraveineuse, même chez des animaux vaccinés, ne se résorbent pas, et cette constatation explique que les bovidés vaccinés par la méthode de von Behring restent pendant de longs mois (plus de six mois dans l'expérience de Melun en 1906,

* Annales de l'Institut Pasteur, octobre 1905, mai 1906, août 1906, et juillet 1907.

Vallée et Rossignol, Moussu) porteurs de bacilles vivants et virulents dan leurs ganglions bronchiques et médiastinaux.

Or, tant que ces animaux restent ainsi porteurs de bacilles, il est impossible de les considérer comme réellement vaccinés. Ils possèdent seulement une résistance spéciale à l'égard de nouvelles infections tuberculeuses et cette résistance est tout-à-fait comparable à celle que Robert Koch a signalée le premier chez les cobayes tuberculeux auxquels on injecte sous la peau une nouvelle dose de virus: la seconde inoculation produit un abcès local qui se vide bientôt, et l'ulcération qui lui succède guérit, tandis que la première infection continue à produire ses effets avec plus de lenteur.

On peut obtenir la même résistance en injectant dans les veines de bovidés sains de fortes doses de tuberculine (0 gr. 50 de tuberculine précipitée par l'alcool) deux ou trois fois à 6 ou 10 jours d'intervalle. Les animaux ainsi préparés réagissent à la seconde ou à la troisième injection comme s'ils étaient tuberculeux. La réaction, toujours très forte, apparaît alors chez eux dès la 5e heure et disparaît à la 12e. Si, quelques jours après la dernière injection tuberculinique, on leur injecte dans les veines 5 milligr. de bacilles bovins virulents en même temps qu'à des témoins sains, on constate que ces derniers prennent une tuberculose granulique à marche suraigüe mortelle en 5 à 6 semaines, tandis que chez tous les animaux préparés par les injections préalables de tuberculine n'apparaissent que des lésions tuberculeuses à évolution très lente.

Les mêmes phénomènes s'observent chez les bovidés déjà porteurs de lésions tuberculeuses spontanées et qui réagissent à la tuberculine. Jamais l'inoculation intraveineuse de bacilles ne détermine chez eux l'apparition de tuberculose granulique aigüe.

Il est donc hors de doute que les animaux tuberculeux et aussi les animaux sains préparés par des injections massives de tuberculine, sont incomparablement plus résistants que les animaux neufs à l'inoculation intraveineuse d'épreuve.

On doit penser que les bovidés vaccinés par voie intraveineuse avec des bacilles humains (von Behring) ou par voie sous-cutanée avec des bacilles bovins ou humains (Lignières), ou sous la peau desquels on troduit des sacs de roseau collodionné contenant des cultures de tuberculose (Heymans), acquièrent par un mécanisme identique une résistance marquée à l'infection tuberculeuse: les bovidés ainsi préparés gardent plus ou moins longtemps les apparences d'une bonne santé; ils perdent fréquemment l'aptitude à réagir à la tuberculine, mais ils n'en restent pas moins porteurs de bacilles et susceptibles de contracter une tuberculose à forme chronique. On ne saurait donc admettre qu'il s'agit là d'une véritable immunité.

En clinique humaine on constate fréquemment des faits analogues. Chacun sait qu'une tuberculose locale suppurée, survenant chez un tuber-

culeux pulmonaire, améliore l'état du malade et accroît considérablement sa résistance. Inversement, il est rare que les sujets chez lesquels la tuberculose pulmonaire évolue avec une marche rapide aient été atteints antérieurement de suppurations ganglionnaires, osseuses ou cutanées, hormis les cas où opération chirurgicale inopportune a pu provoquer une infection sanguine.

Si l'on veut bien se rappeler que certains cliniciens ont prétendu obtenir chez les malades phtisiques de réelles améliorations à la suite d'inoculations sous-cutanées de cultures de tuberculose bovine virulente (F. Klemperer), ou de bacilles morts (Maragliano), ou de cultures de tuberculose humaine modifiée par passages dans l'organisme d'animaux à sang froid (crocodile) (Moeller), les faits expérimentaux qui précèdent sont de nature à justifier dans une certaine mesure leurs assertions.

Mais une telle méthode thérapeutique est assurément condamnable. Elle l'est d'autant plus que nous possédons dans la tuberculine un moyen aussi efficace et moins dangereux permettant d'atteindre le même but.

La inmunización contra la Tuberculosis.—(Calmette y Guérin.)

En una serie de memorias que nosotros publicamos hace ya algun tiempo, nosotros demostramos la posibilidad de producir en los animales jovenes lo mismo que en los viejos (ganado, cabras, cobayos), una marcada resistencia a la infección artificial de la tuberculosis por medio del aparato digestivo. Esta resistencia se obtiene por medio de la alimentación del animal con una emulsión fina del bacilo de la tuberculosis bovina, virulento ó modificado por medio de la aceión del calor á una temperatura de 70° centigrados. En el ganado una sola inyección del bacilo virulento es usualmente suficiente para producir una infección tan ligera que, despues de reaccionar á la tuberculina por el espacio de uno á dos ó tres meses, el animal cesa de reaccionar y es capaz de resistir por mas de un año una gran cantidad, las inyecciones repetidas de dosis del bacilo de la tuberculosis que de seguro infectan a los animales a prueba en observación.

Los animales vacunados por este metodo, continuan por cerca de tres meses a albergar en las glandulas mesentericas bacilos vivos y virulentos capaces de infectar a los cobayos inyectados con la trituración de estas glandulas. Mas tarde los bacilos desaparecen, los cuales no se encuentran después del intervalo de cuatro a seis meses. Si á este tiempo los animales son sometidos á prueba por medio de la inyección intra venosa de una fuerte dosis del bacilo bovino (5 miligramos), y simultaneamente se hace lo mismo con animales en observación de la misma edad, se observa que en los animales en observación se desarrolla una tuberculosis granular ex-

tremadamente râpida, fatal en el intervalo de cuatro á seis semanas; mientras que en los animales vacunados presentan todas las apariencias de estar en buena salud por ocho meses á lo menos; cuando una vez la inmunidad desaparece, como se demuestra por el hecho de que algunos de ellos de repente presentan lesiones tuberculosas en varias localidades; y si aquellos que aun no presentan lesiones algunas son sacrificados, se encuentra que las glandulas en el mediastino y las glandulas bronquiales siempre contienen bacilos vivos y virulentos para el cobayo, aun en las condiciones en que otras lesiones microscopicas sean nulas. Esto es evidente, por lo tanto, que los bacilos introducidos en las venas, aun el los animales vacunados, no son absorbidos, y este hecho explica el por qué las vacas vacunadas por el metodo de von Behring continuan por muchos meses albergando bacilos virulentos vivos en las glandulas del mediastino. Mientras estos animales continuen albergando bacilos no pueden ser concideradas como vacunados. Ellas solamente poseén una resistencia especial contra una nueva infección tuberculosa, una resistencia que es en muchos puntos comparable a la que Robert Koch observó primeramente en los cobayos tuberculosos que habian recivido una inyección subcutanea de una dosis fresca del virus; la segunda inoculación produce un absceso local que pronto se evacua por si solo, y ulceraciones que se curan, mientras que la primera infección continua produciendo sus efectos mas lentamente. La misma infección puede producirse por medio de la inyección intravenosa de tuberculina en le ganado sano (0 gramos. 50 de tuberculina precipitados por medio del alcohol), dos o tres veces á intervalos de seis a diex dias. Animales preparados de esta manera reaccionan a la segunda ó tercera inyección como si estos fuesen tuberculosos. La reacción que se siempre marcada, aparece en tales animales en cinco horas y desaparese al termino de doce horas. Si unos pocos dias después de la inyección de la tuberculina, se administra una inyección intravenosa de 5 miligramos del bacilo bovino virulento, y animales sanos en observacion son simultaneamente sometidos al mismo tratamiento, en los animales en observación se desarrolla una granulación tuberculosa rápida que es fatal en cinco a seis semanas, mientras que en los animales preparados por medio de la inyección previa de la tuberculina, presentan solamente lesiones tuberculosas de progreso lento.

Los mismos fenomenos se observan en el ganado ya afectado con lesiones espontaneas de tuberculosis y que reaccionan a la tuberculina. La injección intravenosa del nacilo, nunca es seguida de la aparición de tuberculosis granular aguda en estos animales. No hay duda, por lo tanto, que animales tuberculosos y animales sanos, preparados por medio de la previas inyecciones de tuberculina, poseen incomparable resistencia mayor á la de los animales que son nuevos a la prueba intravenosa de la inoculacion. Es eviden que el ganado vacunado por las inyecciones intravenosas del bacilo

de la tuberculosis humana (von Behring) ó subcutaneamente por medio del bacilo de origen bovino ó humano (Lignieres) y animales tratados por medio de la introducciún bajo la piel de capsulas hachas de la membrana interna del carrizo, y cerradas con colodion, conteniendo el bacilo de la tuberculosis (Heymans), adqueren por medio de un mecanismo idéntico una marcada resistencia a la infección tuberculosa; el ganado asi preparado preserva la apariencia de una solud perfecta por un periodo de tiempo variable; á menudo pierden el poder de reacción a la tuberculina, mas son, sinembargo, portadores el bacilo y capaces de crear una forma crónica de la tuberculosis. No puede decirce, por lo tanto, que este es un caso de inmunidad.

En el hombre se han hecho observaciones semejantes. Es bien sabido que la supuración tuberculosa local en los tísicos, mejora las condiciones del paciente, y aumenta conciderablemente la resistencia. Al contrario, personas, en las cuales la tuberculosis pulmonar es de una marcha rápida, han sufrido raramente en su previa historia de supuración de las glandulas, los huesos ó de las estructuras cutaneas, excepto en aquellos casos en que una mal calculada operacion quirúrgica haya producido una infección de la sangre. Si se recuerda que en ciertas condiciones se han obtenido mejoras reales después de una inoculación subcutanea de culturas virulentas del bacilo de origen bovino (F. Klemperer), ó de bacilos muertos (Maragliano), ó con culturas de origen humano modificado por medio del pasage de estas en los animales de sangre fria (cocodrilo, Moeller), los hechos experimentales mencionados son calculados hasta cierto punto en justificación de sus aserciones. Tal modo de tratamiento, sinembargo, deberá ser condenado, particularmente cuando se poseé en la tuberculina un remedio igualmente eficiente y menos peligroso con el cual el mismo resultado puede obtenerse.

Immunization Against Tuberculosis.—(CALMETTE AND GUÉRIN.)

In a series of papers published some time ago we showed that it is possible to produce in young as well as old animals (cattle, goats, guinea-pigs) a marked resistance to artificial tuberculous infections by way of the digestive tract. This resistance is obtained by feeding the animals fine emulsions of bovine tubercle bacilli, virulent or modified by heating them to 70° C. In cattle a single ingestion of virulent bacilli usually suffices to produce an infection so slight that, after reacting to tuberculin for one, two, or three months, the animals cease to react and become capable of resisting, for more than a year, the large quantity of

repeated doses of tubercle bacilli which certainly infect the control animals.

Animals vaccinated by this method continue for about three months to harbor, in their mesenteric glands, living virulent bacilli capable of infecting guinea-pigs injected with a triturate prepared from these glands. Later they get rid of the bacilli, which are no longer found after an interval of four to six months. If at this time the animals are tested by means of intravenous inoculations with a strong dose of virulent bovine bacilli (5 milligrams), simultaneously with control animals of the same age, it is found that the controls develop an excessively rapid granular tuberculosis, which proves fatal in from four to six weeks; while the vaccinated animals maintain every appearance of perfect health for at least eight months; then all at once their immunity disappears, as shown by the fact that some of them suddenly present tuberculous lesions in various locations. If those which do not show any lesions are killed, it is found that the mediastinal and bronchial glands contain living bacilli that are virulent for the guinea-pig, even though there may be no other microscopic tuberculous lesion. It is evident, therefore, that bacilli introduced into the veins, even in vaccinated animals, are not absorbed, and this fact explains why cattle vaccinated by von Behring's method continue for many months to harbor living virulent bacilli in their bronchial and mediastinal glands. So long as these animals continue to harbor bacilli they cannot be considered to be really vaccinated. They merely possess a special resistance against fresh tuberculous infections, a resistance which is comparable to that which Koch first observed in tuberculous guinea-pigs that had received a subcutaneous injection of a fresh dose of virus. The second inoculation produces a local abscess which soon empties itself, and the ulceration which follows heals, while the first infection continues to produce its effect more slowly. The same resistance can be obtained by injecting healthy cattle intravenously with large doses of tuberculin (0.50 gm. of tuberculin precipitated with alcohol), two or three times at intervals of six or ten days. Animals treated in this way react to the second or third injection as if they were tuberculous. The reaction, which is always marked, appears in such animals in five hours and disappears at the end of twelve hours. If, a few days after the last injection of tuberculin, an intravenous injection of 5 milligrams of virulent bovine bacilli is administered, and healthy control animals are simultaneously subjected to the same treatment, the controls develop a very rapid granular tuberculosis which proves fatal in from five to six weeks, while animals prepared by previous injections of tuberculin merely present very slowly progressing tuberculous lesions.

The same phenomena are observed in cattle affected with spontaneous tuberculous lesions and reacting to tuberculin. The intravenous injection of bacilli is never followed by the appearance of acute granular tuberculosis in these animals. There is no doubt, therefore, that tuberculous animals and healthy animals prepared by previous large doses of tuberculin, possess incomparably greater resistance than animals which are new to the intravenous test inoculation. It is evident that cattle vaccinated intravenously with human bacilli (von Behring), or subcutaneously with bovine or human bacilli (Lignieres), and animals treated by introducing under the skin capsules made of reed and sealed with collodion, containing cultures of tubercle bacilli (Heymans), acquire, by the identical mechanism, a marked resistance to tuberculous infection; cattle treated in this way preserve the appearance of perfect health for a variable length of time; they often lose their power of reacting to tuberculin, but they are, nevertheless, carriers of bacilli and capable of developing a chronic form of tuberculosis. It cannot be said, therefore, that this is a true immunity.

In human beings similar observations have been made. Every one knows that a local suppurative tuberculosis, occurring in a consumptive, improves the patient's condition and considerably increases his resistance. Conversely, persons in whom pulmonary tuberculosis follows a rapid course have rarely suffered in their previous history from suppuration of glands, bones, or cutaneous structures, excepting those cases in which an ill-advised surgical operation may have produced a blood infection. When it is recalled that certain clinicians claim to have obtained improvement in tuberculous patients by a subcutaneous inoculation of cultures of virulent bovine bacilli (F. Klemperer) or dead bacilli (Maragliano), or of cultures of human bacilli modified by being passed through the body of a cold-blooded animal (crocodile) (Moeller), the above experimental facts are calculated to a certain extent to justify their assertions. Such a mode of treatment is, however, to be condemned, particularly since we possess in tuberculin an equally efficient and less dangerous remedy, wherewith the same object may be obtained.

ÜBER IMMUNISIERUNGSVERSUCHE GEGEN TUBERKULOSE.

Von J. Bartel,
Wien.

Wie ich schon mehrmals Gelegenheit hatte auszuführen, gelang es mir, in Fütterungsexperimenten am Tiere den Nachweis zu führen, dass zwischen dem Tuberkelbazillus und den Organgeweben, speziell den lymphocytären, innige Wechselbeziehungen bestehen. Ja, ich musste auf Grund meiner Beobachtungen namentlich den lymphatischen Geweben eine direkte Schutzwirkung gegenüber der Tuberkulose-Infektion zuschreiben, die genauer zu verfolgen ich mir zur Aufgabe machte. Bei meinen diesbezüglichen Studien standen mir vornehmlich Neumann, dann auch Hartl, als Mitarbeiter zur Seite. So haben wir die *in vivo* von mir gemachten Beobachtungen *in vitro* nachgeprüft und sind hier zu folgenden Resultaten gekommen:

"Wenn Tuberkelbazillen des Typus humanus und bovinus längere Zeit bei 37° C. und bei Abwesenheit anderer Bakterien in Organen gesunder Tiere suspendiert gehalten werden, so bleiben sie zwar lebensfähig, erweisen sich aber, wenn sie mit dem Organgewebe an Meerschweinchen und Kaninchen verimpft werden, als avirulent.

"Solchergestalt geimpfte Tiere lassen, lange Zeit nach dieser Impfung bei Wohlbefinden getötet, jedwedes Anzeichen einer 'manifesten' Tuberkulose vermissen und zeigen fast regelmässig mehr oder weniger deutliche Hyperplasie ihrer lymphatischen Organe.

"Bei einmaliger oder in Zeitintervallen wiederholter Impfung der angeführten Art machen sich an den so 'vorbehandelten' Tieren bei früher oder später folgender virulenter tuberkulöser Infektion gegenüber den in gleicher Weise infizierten Kontrolltieren Immunitätserscheinungen geltend, u. s. w.

"Überempfindlichkeit, erhöhte Resistenz, schliesslich auch volle Immunität.

"Dabei leben die virulent infizierten 'vorbehandelten' Tiere kürzer oder länger als die Kontrolltiere und zeigen, an Tuberkulose verendet, ein von dem bekannten Resultat der Impftuberkulose am 'nicht vorbehandelten' Tiere abweichendes Bild.

"Vorherrschende und auch isolierte manifeste Tuberkulose der Lungen und Bronchiallymphdrüsen bei Zurücktreten der spezifisch tuberkulösen

Erkrankung im Eintrittspfortenbereich, resp. bei 'anscheinend' unverändertem Zustand der Gewebe daselbst. Cavernöse Tuberkulose der Lungen bei Überempfindlichkeit wie bei erhöhter Resistenz. Ausheilungsvorgänge in bereits manifest tuberkulös veränderten Organen. Schliesslich Freibleiben von jeder manifest tuberkulösen Veränderung an allen Stellen des Organismus."

Damit komme ich zu folgendem Schlusse:

"Wir müssen es als erwiesen betrachten, dass es gelingt, eine bestimmte Beeinflussung von Tuberkelbazillen durch Organgewebe, speziell durch lymphatisches Gewebe, zum Ausgangspunkt eines erfolgreichen spezifischen Immunisierungsverfahrens gegen Tuberkulose zu machen."

Dass es gelingt auf Basis der Beziehungen von Organgeweben und Tuberkelbazillen im Tierexperimente auch therapeutische Effekte zu erzielen, darauf wurde bereits früher von mir hingewiesen.

Es kann nicht meine nächste Absicht sein, ein solches Verfahren der Immunisierung gegen Tuberkulose derzeit direkt in die Verhältnisse des praktischen Lebens zu übertragen, doch halte ich die gewonnenen Resultate für geeignet, hinzuweisen auf die gewiss grosse Bedeutung der Organzelle im allgemeinen auch bei anderen infektiösen Prozessen. Es mag das Studium der Wechselbeziehung von Zelle im Organismus und Infektionsträgern verschiedener Natur ja vielleicht noch manches Rätsel zu lösen, gegenüber welchem wir uns gegenwärtig noch vielfach auf dem Boden unfruchtbarer Hypothesen bewegen.

Immunization Against Tuberculosis.—(BARTEL.)

The behavior of tubercle bacilli that have entered the body through natural channels indicates a protective action on the part of the cells of organs, and especially of lymphocytes, against the infection.

In vitro it is possible, with the aid of various organs, especially organs of a lymphocytic nature, to render living tubercle bacilli avirulent by confining them for some time within the organs at a temperature of 38°. This is true of human as well as of bovine bacilli. In the course of attempts to produce immunity on this principle animals have been successfully immunized against an infection which proved fatal to the control animals. Hence the attempt to utilize this action of the tissues of organs on the tubercle bacillus as the basis of immunization against tuberculosis has proved successful.

La Inmunizacion contra la Tuberculosis.—(BARTEL.)

La accion del bacilo de la tuberculosis cuando este entraen el organismo por medio de los canales naturales, indica una accion protectora de parte

de las celulas de los organos, especialmente los linfocitos, contra la infeccion.

En vitro, esto es posible con la ayuda de varios organos, especialmente los organos de naturaleza linfocitaria, de abolir la virulencia del bacilo por medio del confinamiento de este en las celulas de los organos á una temperatura de 38°. Este es el caso con el bacilo de origen bovino lo mismo que con el de origen humano. En el curso de las tentativas de producir la inmunidad basado sobre estos principios, animales han sido con exito inmunizados contra una infeccion fatal para los animales sanos en observacion. Por lo tanto las tentativas en utilizar este accion de los tejidos do los organos en el bacilo de la tuberculosis, como base de la inmunidad contra la tuberculosis, ha dado resultados favorables.

Expériences d'Immunisation contre la Tuberculose.—(BARTEL.)

La conduite du bacille de la tuberculose quand il s'introduit dans l'organisme par les voies naturelles nous fait voir qu'il y a dans les cellules des organes, et surtout dans les lymphocytes, une action protectrice contre l'infection qui a eu lieu.

In vitro on a réussi à l'aide de divers organes, surtout ceux d'une nature lymphocytaire, de rendre avirulents même des bacilles vivants, en les renfermant pendant un certain temps dans les organes à la température de 38°, que les bacilles soient de type humain ou bovin. Dans ces expériences on a réussi à immuniser, d'après ce principe, un animal contre une infection qui amena la mort des contrôles. Donc la tentative d'exploiter cette action protectrice des tissues des organes contre le bacille tuberculeux dans l'immunisation contre la tuberculose a réussi.

CONTRIBUTION A L'ÉTUDE DE L'IMMUNITÉ TUBERCULEUSE.

(RÉINOCULATIONS NEGATIVES.)

PAR MM. LES DOCTEURS JULES COURMONT ET A. LESIEUR,

Lyon.

La réinoculation de la tuberculose en un autre point du corps, chez un animal déjà tuberculeux, donne-t-elle un résultat positif ou négatif? Les avis sont partagés.

Nous avons repris la question sur le *cobaye*, avec des cultures très-virulentes de bacilles bovins, en employant notre méthode *d'inoculation transcutanée de la tuberculose* (Société de Biologie et Journal de Physiologie et de Pathologie générale, 1907). La lenteur de l'évolution, le peu d'importance ou l'absence de lésions locales, la grosseur des ganglions caséeux, constituent des conditions favorables.

Déjà, si on inocule sous la peau un cobaye, tuberculeux depuis 13 à 20 jours, la réaction ganglionnaire est plus faible que chez les témoins; mais ces résultats de l'inoculation sous-cutanée ne sont pas probants.

Les résultats sont très-nets si on fait deux inoculations *transcutanées* (c'est-à-dire en frottant simplement la peau avec des cultures) successives, à quinze jours au moins d'intervalle. La réinoculation est négative. Il ne se produit aucune lésion locale. Les ganglions ne se tuberculisent pas, sont à peine hypertrophiés, ne sont jamais caséeux. Il ne se produit aucune généralisation, ni à la rate ni ailleurs. Par contre, si on laisse vivre les animaux, la première inoculation suit son cours normal; elle s'accompagne de généralisation et finit par tuer l'animal. C'est donc une lésion en évolution qui empeche l'évolution d'une seconde inoculation.

L'homme tuberculeux en évolution est-il donc à l'abri d'une réinfection? *La question est posée par ces expériences.*

Ein Beitrag zum Studium der Immunität gegen Tuberkulose (Negative Reinoculation).—(COURMONT UND LESIEUR.)

Die Reinoculation von Tuberkulose in einen anderen Körperteil eines Tieres, das bereits tuberkulös ist, mag ein positives oder negatives Resultat ergeben, da die Meinungen in diesem Punkte geteilt sind.

Wir haben diese Frage am Meerschweinchen versucht, indem wir sehr virulente Culturen von Rinderbacillen benützten mit unserer transcutanen Inoculationsmethode. Wenn man den Process fortschreiten lässt, werden günstige Bedingungen gefunden, die Unwahrnehmbarkeit oder Abwesenheit von localen Verletzungen und die Grösse der verkästen Drüsen. Wenn ein Meerschweinchen, das durch dreizehn bis zwanzig Tage tuberkulös war, subcutan geimpft wurde, dann ist die Drüsenreaction schwächer als in Controlltieren, aber diese Resultate von subcutaner Inoculation lassen keine Schlüsse ziehen. Die Resultate sind sehr klar bestimmt, wenn transcutane Inoculationen in Zwischenräumen von mindestens zwei Wochen gemacht werden (dies wird erreicht durch einfaches Reiben der Cultur auf die Haut). Die Reinoculation ist negativ; durchaus keine localen Verletzungen werden hervorgerufen; die Drüsen werden nicht tuberkulös, sie hypertrophiren in geringem Masse und sind nie käsig. Keine allgemeine Wirkung wird in der Milz oder sonstwo hervorgerufen. Andererseits, wenn man die Tiere leben lässt, nimmt die erste Inoculation ihren normalen Verlauf. Sie ist von allgemeinen Verletzungen begleitet und tötet schliesslich das Tier. Dies beweist, dass eine Verletzung im Processe der Evolution die Evolution einer zweiten Inoculation verhindert.

Unsere Experimente rollen die folgende Frage auf: Ist ein menschliches Wesen während der Evolutionsperiode einer Reinfection gegenüber immun?

A Contribution to the Study of Tuberculous Immunity (Negative Reinoculations).—(COURMONT AND LESIEUR.)

The reinoculation of tuberculosis at another point on the body of an animal which is already tuberculous may give a positive or a negative result. Opinions on this point are divided.

We have tested this question on the *guinea-pig*, using very virulent cultures of bovine bacilli, with our *transcutaneous method of inoculation.* Favorable conditions are found in the slowness of the process, the insignificance or absence of local lesions, and the magnitude of the caseous glands. If a guinea-pig which has been tuberculous for from thirteen to twenty days is inoculated under the skin, the glandular reaction is feebler than in control animals; but these results of subcutaneous inoculation are not conclusive.

The results are clearly defined when two successive *transcutaneous* inoculations are made at intervals of at least two weeks (this is accomplished by simply rubbing the culture on the skin). The reinoculation is negative. No local lesion whatever is produced; the glands do not become tuberculous; they scarcely hypertrophy, and are never caseous. No general effect is produced either in the spleen or elsewhere. On the other hand, if the animals are allowed to live, the first inoculation runs its normal course;

it is accompanied by general lesions and ultimately kills the animal. This proves that a lesion *in process of evolution* prevents the evolution of a second inoculation.

Our experiments suggest the following question: Is a tuberculous human being during the period of evolution immune to reinfection?

Una Contribución al Estudio de la Inmunidad de la Tuberculosis (Reinoculaciones Negativas).—(COURMONT Y LESIEUR.)

La reinoculación de la tuberculosis en otras partes del cuerpo en los animales tuberculosos, puede dar una reacción positiva ó negativa; las opiniones sobre este punto estan divididas.

Nosotros hemos investigado este punto en los cobayos, haciendo uso de culturas muy virulentas del bacilo de la tuberculosis bovina, y empleando el método de la inoculación transcutánea. Las condiciones favorables consisten en el retardo del proceso, las lesiones locales y la magnitud de las glandulas caseosas son nulas ó poco marcadas. Si un cobayo infectado de tuberculosis durante trece ó veinte días, es inoculado bajo la piel, la reacción glandular es menos marcada que en los cobayos, en observación, los cuales recibieron la misma inoculación; mas los resultados de inoculaciones subcutáneas no son concluyentes. Los resultados son claramente definidos cuando dos inoculaciones transcutáneas se hacen sucesivamente en el intervalo á lo menos de dos semanas (ésta se hace por medio de una unción de la cultura sobre la piel). La inoculación es negativa. Lesiones locales son nulas; les glándulas no son afectadas; éllas se hipertrofian ligeramente, mas nunca llegan a terminar en la degeneración caseosa. El efecto general no se produce en el bazo ni en otra parte del cuerpo; si la vida del animal se prolonga, la primera inoculación presenta el curso normal; las lesiones generales aparecen mas tarde, las cuales finalmente producen la muerte. Esto prueba que una lesion en el *proceso de evolución* previene de la evolucion de una segunda inoculación.

Nuestros experimentos sugieren la pregunta siguiente:—Es, una persona afectada de tuberculosis durante el periodo de la evolucion, immune contra la reinfeccion?

IMMUNITY PRODUCTION BY INOCULATION OF INCREASING NUMBERS OF BACTERIA BEGINNING WITH ONE LIVING ORGANISM.

By Gerald Bertram Webb, M.D., and William Whitridge Williams, M.D.,
Colorado Springs.

In Conjunction with Professor M. A. Barber,
University of Kansas.

At the June, 1908, meeting of the Association for the Study and Prevention of Tuberculosis a brief report was read* relating some experiments in immunizing mice against anthrax, and it was promised that similar experiments relating to the production of immunity against tuberculosis in guinea-pigs would later be reported.

Historical.—The use of the guinea-pig as a laboratory animal for the production of immunity against tuberculosis has been common for many years. Mammalian and avian tubercle bacilli, living (attenuated or virulent) and dead, have been employed for immunity production, as well as bacterial products and so-called sera. Not one of countless experiments has established any certain efficiency. Such inadequacy led some to experiment with other acid-fast bacilli, resembling the tubercle bacillus,—the butter, grass, and manure bacilli,—as well as with the bacilli of cold-blooded animals and mammalian tubercle bacilli modified by their passage through such animals. Some results have shown that some immunity has been produced because of the length of life, over the control animals, of those inoculated after virulent tests, but in general no complete protection has been afforded.[1] Every species of animal is susceptible to certain bacteria and non-susceptible to others.

A knowledge of the principle that one attack of an infectious disease confers some immunity belonged to the ancients, and the virus of diseases such as smallpox in man and rinderpest in animals was used for the production of immunity. Jenner was the first, however, to employ attenuated or weakened virus successfully—the smallpox virus permanently modified by

* "Immunity Production by Inoculation of Increasing Numbers of Bacteria Beginning with One Living Organism," preliminary report, by Gerald Bertram Webb, M.D., and William Whitridge Williams, M.D., of Colorado Springs, Colo.

passage of the disease through the cow. Pasteur's work followed this idea, to prevent disease by protective inoculation of weakened virus, and beginning with cultures of chicken cholera, attenuated by accident, he invented new methods for reducing virulence, and attenuated anthrax bacilli by growth at temperatures higher than those to which they were accustomed, rouget in swine by successive passages through the rabbit, and hydrophobia by a long series of inoculations into rabbits. Some degree of artificial immunity has been produced for pathogenic bacteria by previous inoculations with some other organism, and Pasteur noted that attenuated chicken cholera bacteria would protect chickens against anthrax.

Artificial immunity has been attempted by inoculation of a small number of virulent bacteria, and Chauveau, working with diluted cultures and Algerian sheep, immunized them to anthrax, although the same dosage killed French sheep.

At first the interpretation of the influence of the numbers of bacteria injected met with incredulity. To-day, however, it is dogmatic. Arloing, Cornevin, and Thomas produced immunity in this way against symptomatic anthrax. Peugh inoculated without disaster the diluted virus of clavelée (sheep-pox). Charrin used the dilution method against B. pyocyaneus. In the manufacture of antistreptococcus serum and diphtheria antitoxin examples of this may be seen. Hutyra[2] was successful in repeatedly injecting a calf with virulent bovine tubercle bacilli, by beginning with two milligrams and increasing to one hundred milligrams in seventeen months.

The earnest efforts to immunize animals against tuberculosis began with the discovery of tuberculin by Koch[3] in 1890. Koch[4] later concluded that an anti-bacterial immunity as well as an antitoxic immunity was necessary for protection against, and the treatment of, tuberculosis, and finally produced T. R., which was found to induce the highest immunity of any tuberculin. He found that guinea-pigs could be protected, by previous treatment with T. R., against infection with virulent tubercle bacilli. Others corroborated this, and also found it to prolong the life of infected guinea-pigs.

The outcome of all this work has been to establish the fact that tuberculin—dead tubercle bacilli and their products—can have a specific effect on tuberculous lesions, and sometimes cause them to become encapsulated or even to disappear, and that although this effect is not constant, their proper usage seems to insure an average longer tenure of life, both with cattle[5] and with human beings.[6] More and more, however, it became evident that, with a disease which appeared to yield so low a grade of immunity as does tuberculosis, protection must be obtained against the living virus as well as against its poisons.

Probably the first work done with the living bacillus was that of Dixon[7] with attenuated cultures. He found that animals (guinea-pigs, rabbits,

opossums) inoculated with an old culture containing club-shaped and branching forms of tubercle bacilli would resist subsequent inoculation with virulent organisms. Trudeau,[8] in 1892–93, found that by subcutaneous preventive inoculation of living cultures of avian tubercle bacilli he was able to increase the resistance of a rabbit to infection of living virulent mammalian cultures. His[9] remarks, ten years later, quoted by Pearson,[10] are, as we view this subject, of especial interest. "It was only when I began to make use of living cultures as a protective inoculation that I met any encouraging results, and my experience would indicate that the living germ is essential to what success has been attained in the production of artificial immunity against tuberculosis." De Schweinitz,[11] in 1894, with attenuated cultures of human tubercle bacilli, a twentieth generation on glycerin-beef-broth of slightly acid reaction, immunized guinea-pigs so that they remained well following the injection of tuberculous material from a cow, when control animals died with tuberculosis in seven weeks. De Schweinitz also injected, in increasing doses, human tubercle bacilli into cattle, and obtained toleration. McFadyean[12] concluded from bovine experiments that "whatever may have been the degree of natural immunity possessed by these three experimental cattle, it was much increased by the successive intravenous inoculations to which they were subjected. The immunity was not absolute, but it may be doubted whether a degree of resistance that will merit this term is obtainable by any method in cattle." E. Levy[13] immunized guinea-pigs against tuberculosis by giving several inoculations of tubercle bacilli, weakened by glycerin. Pearson and Gilliland[14] showed that the intravenous injections of living human tubercle bacilli were harmless to cattle, and would protect these animals against subsequent inoculations with the bovine bacilli, and were the first to prove that the systematic preliminary treatment with human tubercle bacilli alone would procure this immunity. Von Behring[15] and also Thomassen[16] have obtained similar results, and to von Behring belongs the credit of first proposing a definite method for the practical application of vaccinating cattle against tuberculosis. Neufeld,[17] after thorough trials, abandoned attempts to immunize experimental animals with toxins and dead tubercle bacilli, and produced immunity by the use of living attenuated tubercle bacilli of both human and bovine type. He also pointed out the possibility of overvaccinating, especially in goats. Too large doses of human tubercle bacilli produced little immunity. Neufeld usually preceded the injection of living organisms with injections of pulverized bacilli. The most extensive experiments to ascertain if the human tubercle bacillus could bring about curative effect over existing early lesions of tuberculosis were made by Pearson and Gilliland.[18] Theobald Smith,[19] in quoting their work on calves, writes that the evidence presented by their experiments goes to show that it is possible to arrest tuberculosis, but not to rid the animal of living bacilli. Theobald

Smith has succeeded with a carefully tested attenuated bovine culture in obtaining, in a single injection, as good results as were obtained by double vaccination with living human bacilli. Similar work has been done by Koch[20] and his co-workers.

Importance of Using the Living Virus.—Sustained by the results in diphtheria, the hope that all infectious diseases would be combated by the use of antitoxins has not been realized, and investigators are returning to the use of vaccines for the prevention and cure of these diseases.

By means of cultures of typhoid bacilli, killed in a manner which least harms the protoplasm, Wright[21] has obtained a marked degree of protection to typhoid. This success unfortunately has not accompanied similar attempts with other diseases, although a good measure has been reached therapeutically in the treatment of some infections (staphylococcus, gonococcus).

In addition to other failures in the production of immunity to tuberculosis with dead bacilli must be mentioned Theobald Smith's[19] experience. Bovine cultures, killed at 60° C. for from forty to sixty minutes, and then inoculated in the strength of five to ten times that of living human tubercle bacilli which had given immunity in cattle to the bovine bacillus, failed to produce any appreciable resistance in the experimental animals.

The discovery of healed or healing tuberculous foci in 70 to 90 per cent. of all autopsies,[22] in contrast to the 15 to 20 per cent. of deaths from tuberculosis, shows that susceptibility and immunity are subject to marked individual variations. The ability of an individual to overcome a tuberculous infection is referred in a vague way to an unusual resistance on his part, and the bacilli may have gained foothold during a temporary decline of this resistance. The great majority of mankind must have, in some degree, a natural immunity against tuberculosis. Were it not so, the race would long ago have become nearly extinct. From what we are learning from the opsonic index, this natural immunity is sometimes fortified by subsequent autoinoculation in early infection, resulting in the healed lesions.

It is established that vaccination of calves with the human type of the tubercle bacillus is harmless, and gives them a relatively high resistance to fatal doses of the bovine variety. The immunity produced, however, has not appeared entirely satisfactory in regard to degree and duration, and should probably be fortified by a subsequent injection of bovine bacilli.

To the success in smallpox and in rabies must be added the work of Strong[23] in immunization against plague. The whole story of immunization has led investigators to expect a solution of tuberculosis immunity through the use of living virus.

Should the necessity for the introduction of the living virus in tuberculosis be granted, the natural question arises, "What form will it take, and by what route shall it be introduced?" Let us consider the last question first.

It is known that the same dose of a virulent culture or vaccine can cause death or simply protect, according to the site selected for introduction of the organism. Roche-Lubin observed that the process of immunizing to sheep-rot by feeding was less deadly than by the lancet method. Forty years ago cattle were immunized against "peripneumonia" by the procedure of Willems, which consisted in introducing serum from the pulmonary lesions into the end of the tail. It was found that the local tumefaction was slight and that death was not nearly so frequent as when the inoculation was made into the main body. Chauveau immunized cattle to the same disease by injecting directly into the veins. Chauveau and Arloing found that intravenous injections of bacillus septicus immunized donkeys and dogs, whereas subcutaneous inoculations were fatal. Attempts to immunize cattle by feeding tubercle bacilli have been made by Calmette[24] and Guerin, who also produced some degree of immunity in guinea-pigs by feeding to them certain cold-blooded tubercle bacilli.

Most bovine immunization has been by intravenous injection. Several experimenters, however, have tried subcutaneous injection. Baumgarten,[25] Lignières,[26] and Hutyra[27] favor this method. Theobald Smith[28] very correctly makes the suggestion that it is of importance to ascertain if the lungs, the most frequently affected organs, in the spontaneous disease, and which receive most of the vaccine by the intravenous method, are as well protected by the one as the other method. In all our work the subcutaneous has been the route employed, and in no case has there been formed at the place of injection any permanent lesion, either tumor or any focus discharging tubercle bacilli.

And now to consider the question as to what form the virus must take so that safe immunization can be achieved. All conceivable forms of attenuation of tubercle bacilli cultures have been tried, and of these attenuated cultures minute amounts by weight have been inoculated, and we think perhaps the result of part of our work and that of others we will quote will explain why all these methods have failed.

The work of Gebhardt[29] suggests that the inhalation of four hundred tubercle bacilli can cause tuberculosis in a guinea-pig. Preyss[30] found on one occasion the inhalation of only thirty-six bacilli were necessary, and another time forty-eight. Lately Findel,[31] with more accurate methods of enumerating the numbers inhaled, places the number at sixty-two. But he found that even twenty bacilli could produce infection, and makes the suggestion that possibly only one bacillus is sufficient to infect young guinea-pigs. Findel also concluded that the mortal dose taken by the digestive tract would be at least six thousand times the number inhaled. Ziesché,[32] in reviewing this work, is of the opinion that it is more than probable that, everything being taken into consideration, we must allow the same number (although it per-

haps may be more) inhaled to be able to infect man. Flügge[32] agrees with this.

The virulence of the bacilli would need some consideration in making absolute deductions, but the point we wish to emphasize from these investigations is the few bacilli which are necessary to bring about infection. One of our results will show that five tubercle bacilli, followed a few days later by fifteen,—in all, twenty bacilli,—produced tuberculosis, following subcutaneous inoculation in a guinea-pig. One hundred and fifty bacilli of a culture more attenuated produced a similar result. Wyssokowicz[33] has stated that eight tubercle bacilli have been able to set up an infection in the peritoneal cavity of the guinea-pig, and that twenty-four to thirty are required in the rabbit. It would scarcely, then, be possible to bring about such attenuation for immunization that amounts by dilution or weight could be safely used unless such doses were accurately counted.

In a true vaccination the virus should multiply in the tissues after inoculation. Strong[23] found, in the production of immunity against plague, that the organisms after inoculation had reproduced themselves in the tissues for probably one hundred or more generations within twenty-four hours. This initial growth of bacteria after inoculation, and before the organism prevails over them, is perhaps the chief cause of superiority of the use of the living over dead bacteria.

Welch* long ago suggested that the toxins necessary to produce immunity in some diseases are not elaborated by the bacteria when growing on artificial media, but only within the living body in response to the stimulus of the protective substances secreted by the living cells in their effort to destroy the invaders. We have not been able to study the question as to whether growth of the tubercle bacilli took place subsequent to inoculation. The rate of growth of what will be designated "Culture B"—a somewhat attenuated culture, however—was studied.

Into six microscopical drops of glycerin-veal-broth, single bacilli were introduced, and after fifteen hours' incubation five out of the six had doubled, and the sixth bacillus had multiplied into three bacilli. These bacteria were briefly exposed to the light from an Argand gas-burner, which illuminated the microscopical field in all our work. This experiment, apart from demonstrating the rapidity of reproduction, also gave us satisfactory evidence that our bacilli were alive. The rate of growth in the tissues of the guinea-pigs, however, cannot be estimated from this result, but the chances are probably against reproduction when only one bacillus has been introduced.

* Dr. Welch's hypothesis: "Looked at from the point of view of the bacterium, as well as from that of the animal host, according to the hypothesis advanced, the struggle between the bacteria and the body cells in infections may be conceived as an immunizing contest in which each participant is stimulated by its opponent in the production of cytotoxins hostile to the other, and thereby endeavors to make itself immune against its antagonist."

TABLE I.—ANTHRAX EXPERIMENTS. (MICE.)

Animal Number.	Initial Inoculation.	
1	1 thread.	2 days, dead, no evidence of anthrax.
2	1 thread.	4 days, 2 threads; 8 days, 3 threads; 12 days, 12 threads.
3	1 thread.	3 days, 2 threads; 12th day, 12 threads.
4	2 threads.	8 days, 12 threads.
5	3 threads.	Escaped 4th day.
6	4 threads.	Gave birth 4th day to 7 young. Escaped 5th day.
7	3 threads.	12 threads, 5 days.
8	3 threads.	12 threads, 5 days.
9	6 threads.	12 threads, 4 days; 25 threads, 9 days Dead, anthrax bacilli in tissues.
10	6 threads.	12 threads, 4 days.
11	6 threads	12 threads, 4 days.
12	6 threads.	12 threads, 3 days; 50 threads, 9 days.
13	12 threads.	
14	1 loopful 20-hour broth culture, injected by same technic.	2 days, dead, anthrax bacilli in blood and spleen. Cultures made.
15	100 threads, culture from 14.	
16	250 threads, culture from 14.	Dead, anthrax bacilli in blood and spleen. Cultures made.
17	150 threads, 3d generation from 14.	
18	200 threads, 3d generation.	
19	0.04 c.c. emulsion in broth, same technic.	Dead, anthrax bacilli recovered for culture.
20	0.1 (18μ) thread direct from 19 blood.	3 days, dead, anthrax bacilli in tissues.
21	1 (57μ) thread direct from 19 blood.	3 days, dead, anthrax bacilli in tissues.
22	1 (3μ) thread from 19 culture.	
23	1 thread with 12 spores from 19 culture.	14 days, 68 spores, with about 14 rods. 17 days, dead, anthrax bacilli in tissues.
24	20 (483μ) threads from 17-hour agar culture, from 1st generation from mouse dead of anthrax.	
25	1 (18–21μ) thread from heart's blood of dead mouse, after washing in salt solution.	5 days, dead, anthrax bacilli in tissues.
26	1 (16μ) thread from heart's blood of dead mouse, after washing in salt solution.	5 days, dead, anthrax bacilli in tissues.
27	27 (666μ) threads from 17-hour agar culture from 1st generation from mouse dead of anthrax.	5 days, 1 (18–24μ) thread directly from heart blood dead mouse.
28	70 spores and fragments grown in blood of infected mouse, washed in salt solution.	4 days, dead, anthrax bacilli in tissues.
29	9 spores and few degenerate rods, washed in salt solution, 24 hours, from blood of infected mouse.	5 days dead, anthrax bacilli in tissues.

Experimental Technic.—Emulsions were first made from the cultures, and bacteria were selected from hanging drops of these, according to the

method of Barber.[34] Inoculations were made direct from the isolating pipette, either by introducing the capillary end through a needle puncture of the skin or else by drawing back the fluid containing the bacteria further into the tube, and when at a safe distance making an inoculating point, with a peep flame, which could easily be inserted. Frequently additional broth would be introduced back of that containing the bacteria, to insure a thorough flooding out of the contents. In all cases of anthrax work, plain broth, and in tubercle work glycerin veal-broth, were used.

There is very little doubt as to the inoculation of the single bacterium, as some of the experiments themselves will indicate. Moreover, single bacteria have been selected and placed and stained on an ordinary glass slide, selected and ejected as in the inoculations. These have been stained and found and examined with the oil-immersion lens. From other cultures, such as typhoid, single bacteria have been isolated and new cultures started from them. Single cocci have been worked with and a single influenza bacillus successfully isolated. In the use of small numbers the error in counting was exceedingly slight, and the error in counting the higher numbers, although greater, was still inconsiderable. For quite large doses (many thousands) the emulsions might be standardized by Wright's methods for counting vaccine.

All mice were inoculated subcutaneously at the root of the tail; almost all guinea-pigs subcutaneously in the abdominal region; all rabbits subcutaneously in the back.

When not otherwise stated, it is to be understood that the animal survived.

It will be noticed that one thread (3 to 6 bacilli), isolated direct from blood of a mouse dying from anthrax, on four distinct occasions caused death when inoculated into a fresh mouse.

Nos. 22, 24, and 27 also survived eating the contents of the thorax of No. 28, following death from anthrax.

One thread (18μ) means one thread eighteen micromillimeters long, approximately five or six organisms.

One of these threads was isolated and stained on the slide, and the number of segments counted.

Apparently the minimum lethal dose lies between 6μ and 18μ, and lies below nine spores grown in the blood of an infected mouse.

Mouse No. 27 evidently obtained some immunity from the first inoculation, resisting one thread (18 to 24μ) obtained directly from the heart blood of mouse dead with anthrax. One young rabbit was inoculated with three threads direct from peritoneal fluid of dead mouse 19 and survived.

We are allowed to mention some more recent work done by Professor Barber since leaving our laboratory.

Unless otherwise stated, the rods used were taken directly from heart's blood of infected animal, and the spores used were grown in hanging drops in blood of infected animal, plus salt solution or broth. Spores formed usually less than twenty-four hours after starting culture, and temperature of 37° C. used. In all deaths except 21, anthrax bacilli were found in the blood.

TABLE II.—EXPERIMENTS OF PROFESSOR BARBER.

No.	First Inoculation.	Further Inoculation with Intervals.
1	Lethal dose, death after 2 days.	
2	1 thread (6μ), death after 2 days, anthrax bacilli in organs.	
3	1 thread (9μ), interval 6 days.	1 (21μ), interval 10 days, 1 (40μ), alive 13 days after last inoculation.
4	1 thread (30μ), interval 7 days.	1 (18μ), interval 9 days; 1 (40μ), alive 13 days after last.
5	1 spore, interval 7 days.	2 spores, interval 8 days; 3 spores, interval 8 days; 5 dried spores, alive 4 days after last.
6	1 spore, interval 7 days.	4 spores, interval 7 days; 8 spores, interval 8 days; 12 dried spores, alive 4 days after last. (Nos. 5 and 6, last inoculation dried spores used.)
7	2 spores, after interval 4 days.	Anthrax bacilli found in tissues after death.
8	4 spores, after interval 4 days.	Anthrax bacilli found in tissues after death.
9	20 spores, after interval 3 days.	Anthrax bacilli found in tissues after death.
10	35 spores, after interval 2 days.	Anthrax bacilli found in tissues after death.
11	3 spores, interval 12 days.	6 spores, alive after 12 days.
12	14 spores, interval 12 days.	20 spores, alive after 12 days.
13	1 (9μ), interval 10 days.	11 (27μ), dead after 4 days.
14	1 (7½μ), interval 10 days.	11 (27μ), alive after 13 days.
15	4 spores, dead after 9 days, anthrax.	
16	1 (6μ), alive after 22 days.	
17	1 (21μ), interval 13 days.	III (84μ) plus 2 spores, alive after 7 days. (Here growth in hanging drop used first.)
18	1 (36μ), interval 13 days.	IV. (84μ) plus 2 spores, alive after 7 days. (Here growth in hanging drop used first.)
19	1 (12μ), alive after 21 days.	
20	1 spore, alive after 20 days.	
21	1 spore, died after 11 days. No anthrax found in blood or tissues.	
22	1 spore, alive after 20 days.	
23	2 spores, alive after 20 days.	
24	1 spore, alive after 18 days.	
25	3 spores, alive after 18 days.	
26	4 spores, alive after 18 days.	
27	1 (12μ), alive after 17 days.	
28	1 (6μ), alive after 17 days.	
29	Lethal dose apparently from blood of guinea-pig, alive after 17 days.	
30	2 spores, alive after 16 days.	

TABLE II.—(*Continued.*)

No.	First Inoculation.
31	Lost.
32	1 (36μ).
33	Lethal dose, died, 1 day.
34	1 (12μ), dead after 3 days.
35	1 (9μ), alive after 13 days.
36	1 (12μ), alive after 13 days.
37	11 (57μ), alive after 13 days.
38	Lost.
39	1 (9μ), alive after 10 days.
40	11 (57μ), alive after 10 days.
41	Large dose, degenerated rods, alive after 8 days.
42	2 spores in mother cells, alive after 17 days.
43	3 spores linked together in mother cells, alive after 7 days.
44	4 spores linked together in mother cells, alive after 7 days.
45	111 (93μ) plus 2 spores of first growth in hanging drop, alive after 7 days.
46	11 (57μ) plus 3 spores of first growth in hanging drop, alive after 7 days.
47	15 spores, dried, kept in refrigerator about 10 days before inoculation. Same lot of spores of which 4, when fresh, were fatal to No. 13. These spores proved capable of germination. No. 47 is alive after 4 days.
48	4 spores like those of 47, alive after 4 days.
49	1 spore like those of 47, alive after 4 days.
50	75 to 100 spores like those of No. 47, alive after 4 days.

ANTHRAX. GUINEA-PIG SERIES.

Guinea-pig A. 5 spores (same lot of which killed mouse No. 15), dead after 5 days, anthrax.

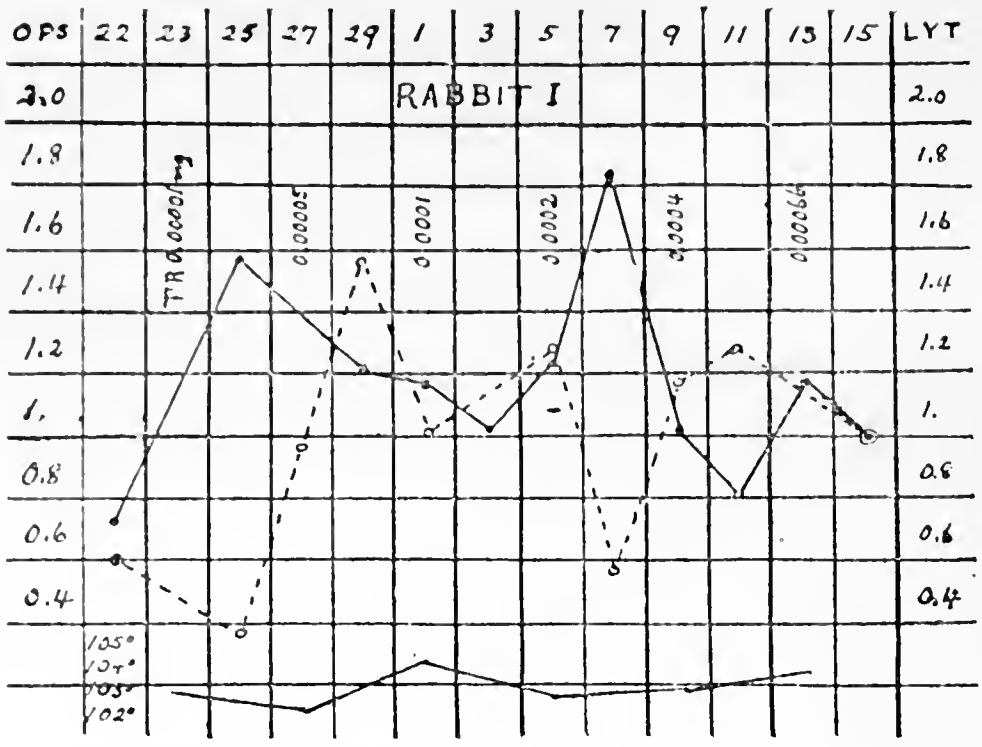
Guinea-pig B. 1 (29μ), interval 5 days; 11 (51μ), alive after 17 days.

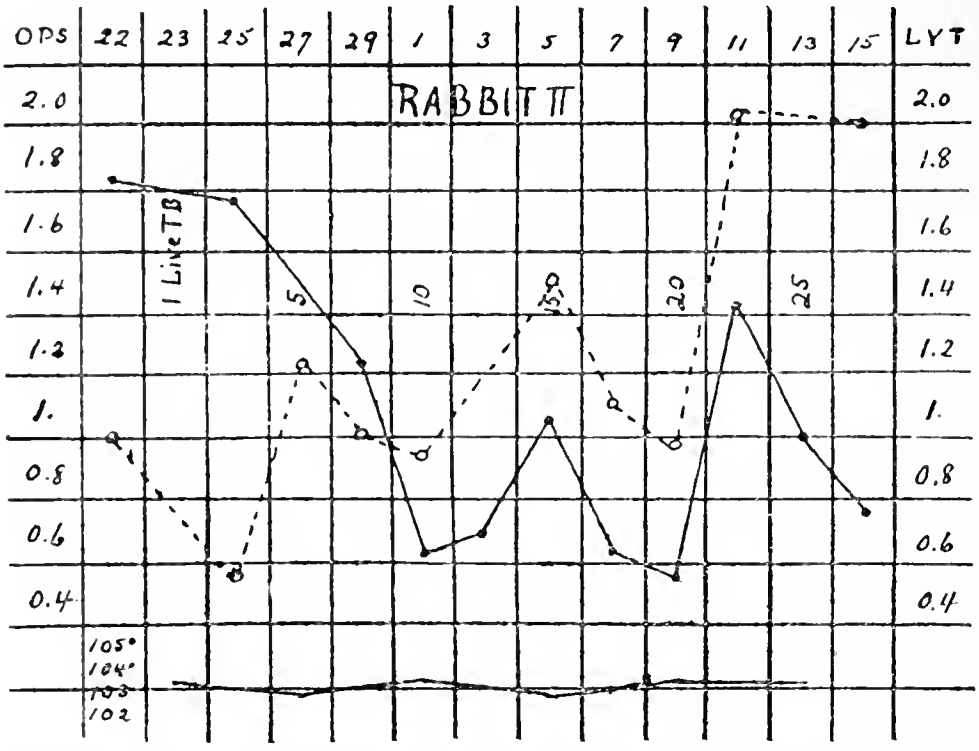
Guinea-pig C. 1 (15μ), directly from blood of guinea-pig A, alive after 17 days. Showing a greater degree of immunity than the mouse.

From the foregoing work, it is evident that we have nothing to show that it is possible to immunize mice with virulent anthrax by graduated doses if bacteria are taken direct from the blood of a mouse dying of anthrax, but the attenuation produced by twelve hours on agar of these same bacilli allows it.

TABLE III.—RABBITS INOCULATED WITH HUMAN TUBERCLE BACILLI.

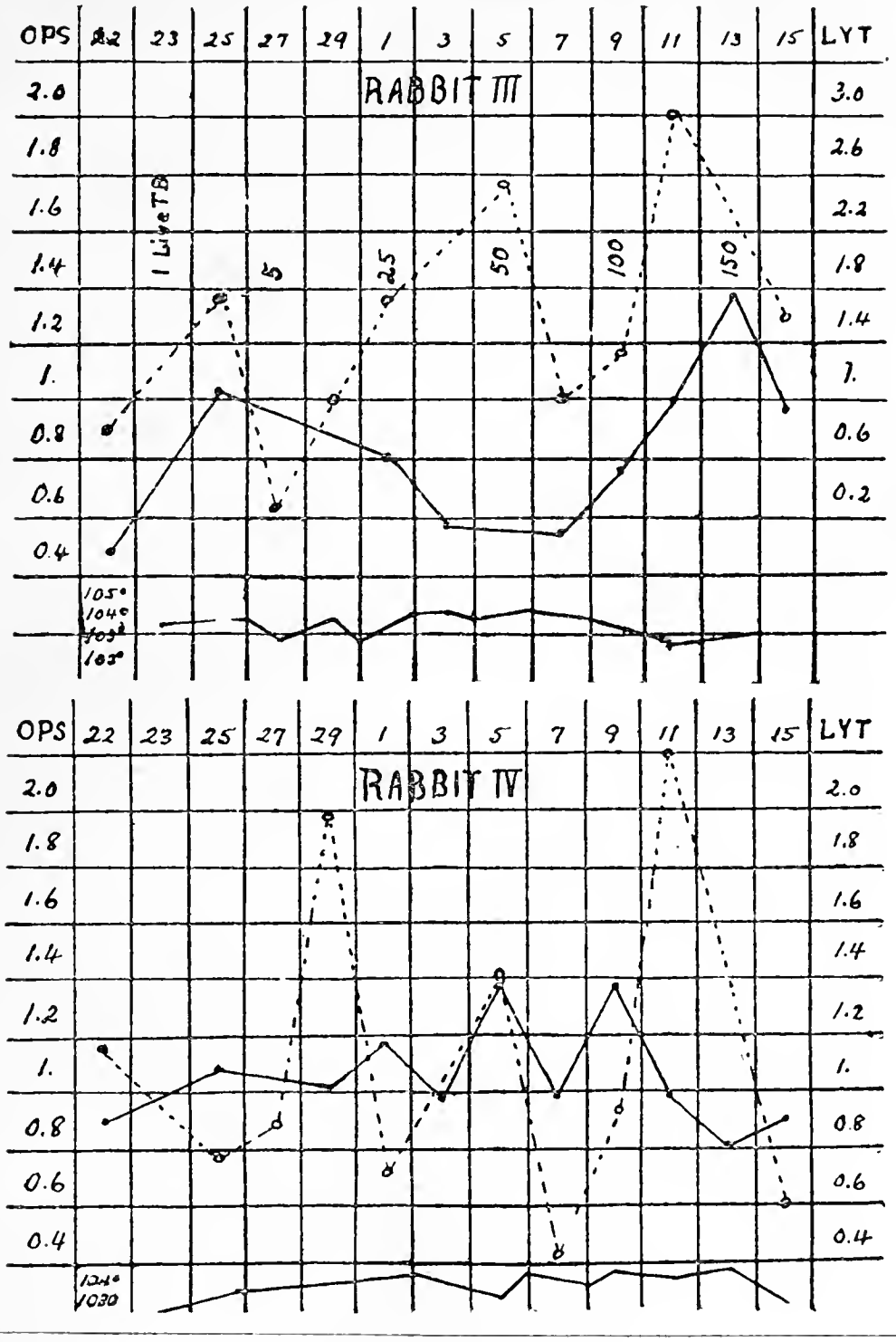
Rabbit Number.	First Day.	Third Day.	Fifth Day.	Ninth Day.	Fifteenth Day.	Section.
1	1 T.B. (A).	5 T.B. (A).	..	25 T.B. (A).	100 T.B. (A).	90th day, no evidence of tuberculosis.
2	1 T.B. (A).	..	..	5 T.B. (A).	..	90th day, no T.B.
3	25 T.B. (A).	..	45 T.B. (A).	..	..	86th day, no T.B.
4	25 T.B. (A).	50 T.B. (A).	..	..	..	84th day, no T.B.
5	1 T.B. (B).	..	..	..	..	80th day, no T.B.
6	1 T.B. (B).	..	..	..	..	77th day, no T.B.
7	25 T.B. (B).	..	..	..	..	75th day, no T.B.
8	1,000 T.B. (B).	..	..	..	..	60th day, no T.B.





The work on rabbits was undertaken while awaiting a new consignment of guinea-pigs. Rabbits have been extensively used to test the immunizing and curative effects of various tuberculins, but we are aware they already possess a marked degree of immunity to the human tubercle bacillus.

Our experiments seem to corroborate this. Work, however, with the bovine bacillus, which will be of greater value, is being prepared for at the present time.



Explanation of Rabbit Charts.

An emulsion of virulent human tubercle bacilli was injected by catheter into the stomach of the four rabbits six weeks previously.

Rabbit I received inoculations of tuberculin.

Rabbits II and III received inoculations of living bacteria.

Rabbit IV was kept as a control.

Fluctuations of both opsonic and lytic indices are to be observed. In rabbit II and rabbit III a general increase in the lytic power is to be observed, following the inoculations of the living tubercle bacilli, in contrast to that observed in rabbits I and IV.

Professor Barber has since inoculated a guinea-pig with one tubercle bacillus taken direct from an infected hog. After thirty-eight days no lesion at autopsy.

In the interpretation of Table IV, "d" means day, "T.B." means tubercle bacillus or tuberculosis, "(1)," tubercle bacillus isolated two months earlier from an active case of pulmonary tuberculosis, originally on Hesse's formula (Heyden's Nährstoff), from this to glycerin-agar with egg-yolk. "(A)" indicates virulent tubercle bacillus culture H 39, obtained through the kindness of Dr. E. R. Baldwin, Saranac. It was isolated directly from sputum of an acute pulmonary case on Hesse's agar, October 3, 1906, thence to egg tubes October 16, 1906, thence to beef serum, with monthly transfers since.

When not specified, a culture of tubercle bacillus (B) obtained from Parke-Davis was used. These gentlemen are not able to tell us the exact origin of this culture, but know it originated either from one supplied them by Dr. Theobald Smith or by Dr. Trudeau. We preferred using culture "B" because it emulsified more easily, and we were the more easily able to avoid clumps.

Eight-tenths of a cubic centimeter of an emulsion of culture "B" was injected into a guinea-pig by the same technic as that employed in the rest of the work; twenty-seven days later tubercle bacilli were taken from an inguinal gland. The exact day of death, however, was not recorded.

(+) signifies the bacilli were especially selected on account of certain refringent characteristics. The bacillus given in No. 10 had a dot in one end. These bacilli usually contrasted strongly with their fellows.

(*) This bacillus was shaped like a spermatozoön.

From A and B fresh cultures were grown every few weeks on glycerin-agar containing egg-yolk, this being the medium on which they thrived best.

In not one of the pigs was a lesion found at the inoculated site at autopsy, and only once or twice could a nodule be felt following an inoculation. Several of our pigs died or were killed because of an epidemic gastro-enteritis. Those referred to as lost were unfortunately stolen from their cages. No pig apparently gave evidence of any condition resulting from anaphylaxis due to the repeated injections of the small amounts of glycerin-veal-broth in which the bacilli were conveyed. The reason for using glycerin-veal-broth in the pipette was to insure the bacilli remaining alive.

The table of the guinea-pig series speaks for itself. The fact that No. 3 proved tuberculous following only twenty bacilli inoculated, although a solitary instance, indicates the necessity for beginning with one bacillus. Culture "A" was more virulent than culture "B." The minimum dose of culture "B" producing tuberculosis appeared to be one hundred and fifty bacilli. In all cases in which the initial dose was one bacillus the pigs

remained free from tuberculosis, even receiving final doses of 1000 or 1500.

In making the autopsies, smears were made from the inguinal glands usually, and stained by the Ziehl-Neelsen and Gram stains. Sections were made for microscopical examination of suspicious areas in different organs. The work of Lannelongue[40] suggests that microscopical examination is not sufficient to show absence of tuberculosis, and that different tissues should be injected into fresh guinea-pigs. We were not able to do this on account of scarcity of pigs.

TABLE IV.—GUINEA-PIG SERIES.

Number of Guinea-pig.	Initial Inoculation	Section.
1	1 T.B. (1).	104th d, no T.B.
2	2 T.B. (1); 29th d, 10 (A); 34th d, 25 (A); 44th d, 75 (B); 55th d, 100; 63d d, 500; 75th d, 750; 85th d, 1,000; 89th d, 1,250; 95th d, 1,500. Total no. bacilli, 5,212.	110th d, no T.B.
3	5 T.B. (A); 4th d, 15 (A). Total no. bacilli, 20.	83d d, T.B. in inguinal glands.
4	5 T.B. (A); 4th d, 15 (A); 9th d, 50 (A); 18th d, 150 (B); 29th d, 250; 37th d, 500; 68th d, 700. Total no. bacilli, 1,670.	68th d, following abortion, no T.B.
5	25 T.B. (A); 4th d, 50 (A); 9th d, 100 (A); 18th d, 200; 28th d, 300; 36th d, 525; 45th d, 800; 51st d, 1,000. Total no. bacilli, 3,000.	60th d, no T.B.
6	25 T.B. (A).	55th d, no T.B.
7	50 T.B. (A); 9th d, 100; 19th d, 200; 27th d, 500. Total no. bacilli, 850.	51st d, no T.B.
8	50 T.B. (A).	76th d, no T. B.
9	1 T.B.	Lost.
10	1 T.B. (+); 4th d, 5.	52d d, no. T.B.
11	1 T.B. (+).	Lost.
12	1 T.B.; 4th d, 5; 9th d, 25; 11th d, 50; 19th d, 150; 25th d, 300; 31st d, 600. Total no. bacilli, 1,131.	39th d, no T.B.
13	1 T.B.; 4th d, 5; 9th d, 25; 22d d, 75. Total no. bacilli, 106.	Lost.
14	1 T.B; 4th d, 5; 10th d, 60; 15th d, 150; 19th d, 300; 23d d, 450; 31st d, 600; 39th d, 750; 44th d, 900; 49th d, 1,050. Total no. bacilli, 4,266.	74th d, no T.B.
15	1 T.B.; 2d d, 10.	69th d, no T.B.
16	1 T.B.	37th d, no T.B.
17	1 T.B.; 2d d, 5; 9th d, 10; 14th d, 50; 22d d, 100; 31st d, 200; 37th d, 300; 42d d, 400.	Lost.
18	1 T.B.; 2d d, 10; 9th d, 25; 17th d, 40; 24th d, 60; 31st d, 85. Total no. bacilli, 221.	39th d, no T.B.
19	1 T.B.; 2d d, 10; 9th d, 25; 14th d, 50; 23d d, 75; 31st d, 100; 37th d, 125; 42d d, 150. Total no. bacilli, 536.	61st d, no T.B.
20	1 T.B.	61st d, no T.B.
21	100 T.B.; 15th d, hard nodule at inoculation site, which later disappeared.	33d d, no T.B.

TABLE IV.—GUINEA-PIG SERIES.—(*Continued.*)

Number of Guinea-Pig.	Initial Inoculation.	Section.
22	100 T.B.; 10th d, 200; 14th d, 300; 23d d, 400; 30th d, 500; 36th d, 600; 41st d, 700. Total no. bacilli, 2,800.	52d d, no T.B.
23	.8 c.c. emulsion, culture (B).	
24	150 T.B.	62d d, lungs full of tubercles.
25	150 T.B.; 7th d, 300; 11th d, 450; 20th d, 600; 28th d, 750; 34th d, 900; 39th d, 1,050.	Lost.
26	1 T.B.; 5th d, 5; 11th d, 10; 19th d, 15; 28th d, 20; 34th d, 25; 39th d, 30.	66th d, no T.B.
27	1 T.B. (+); 5th d, 5; 14th d, 15; 19th d, 25.	26th d, no T.B.
28	1 T.B. (+); 5th d, 5; 11th d, 80; 21st d, 150; 30th d, 250; 34th d, 350; 40th d, 450. Total no. bacilli, 1,286.	65th d, no T.B.
29	1 T.B. (+); 5th d, 5.	60th d, no T.B.
30	1 T.B. (*).	62d d, no T.B.
31	320 T.B.; 5th d, 1,000; 18th d, 2,000. Total no. bacilli, 3,320.	26th d, no T.B.
32	300.	60th d, no T.B.
33	500; 12th d, 1,000; 22d d, 3,000; 27th d, 5,000; 33d d, 7,000.	Lost.
34	500.	22d d, no T.B.
35	500; 12th d, 2,500. Total no. bacilli, 3,000.	32d, d, no. T.B.
36	500; 12th d, 3,500; 16th d, 6,500; 22d d, 9,500; 29th d, 11,500.	General tuberculosis.
37	1,000.	Tubercles in spleen.
38	1,000; 9th d, 1,500; 17th d, 2,000; 20th d, 2,500; 26th d, 3,000. Total no. bacilli, 10,000.	Tubercles in lungs and liver.
39	2,000.	16th d, death due to a septicemic lymphangitis, spreading from inoculation site.
40	2,000; 8th d, 3,000; 20th d, 4,000; 25th d, 5,000. Total no. bacilli, 14,000.	50th d, tubercles in lungs and liver.
41	3,000.	51st d, tubercles in lungs and liver.
42	3,000; 7th d, 4,500; 15th d, 6,000; 20th d, 7,500; 25th d, 9,000. Total no. bacilli, 30,000.	51st d, tubercles in lungs, liver, and spleen.
43	4,000.	48th d, tubercles in lungs and spleen.
44	4,000; 15th d, 6,000; 21st d, 8,000. Total no. bacilli, 18,000.	46th d, no T.B.
45	1 T.B. obtained from inguinal glands of No. 23 on the 27th day after inoculation of. 8 c.c. emulsion of culture B.	46th d, no T.B.

Evidences of Immunity from the Foregoing Experiments.—From the work with mice and guinea-pigs a remarkable degree of individual susceptibility and resistance to anthrax and tuberculosis will be noticed. This variation in the degree of natural immunity to bacteria no doubt must be counted with in all experimental work with laboratory animals.

The fact that large doses—numbers many times beyond those possible to produce disease in individual animals—were safely inoculated and the

consideration of the total number of bacteria altogether inoculated must indicate some degree of successful immunity.

Strong[23] found, in immunizing monkeys against plague, that when they are able to resist and survive over twelve times the maximum fatal dose, agglutinins could not be demonstrated in their blood. Only small quantities of agglutinins could be detected in the examinations of several test immune sera prepared from horses, and which were known to possess considerable protective power. Strong says: "In conformity with the experiments of Kolle and Hetsch, and more recently Dean, I have found that plague-immune serum which is known to possess anti-infectious power in the animal reveals in vitro no bacteriolytic action. I have been able to show that the blood-serum of both human beings and animals vaccinated and immunized against pest frequently revealed an increased opsonic index, although not invariably."

Our blood tests in the tuberculosis experimental animals resulted in a similar manner. With some of the guinea-pigs we undertook to attempt to estimate the amount of opsonin and lysin. The blood was procured direct from the heart, and high opsonic indices were found in guinea-pigs later shown to be decidedly tuberculous. For instance, No. 37 gave indices of 2 and 1.9, whereas guinea-pig No. 2 gave an index of 1.

The amount of lysin was estimated by what was suggested by one of us[41] as a possible lytic index method. The guinea-pigs were found not to vary, whereas men inoculated in a similar manner showed variations amounting to several times the lysin contained in normal sera, when their opsonin was normal.

It is known that phagocytosis in the guinea-pig occurs very readily, and it is perhaps possible that a guinea-pig and man depend upon a different principle of defense to tuberculosis. It may be recalled that in anthrax dogs owe their immunity to phagocytosis and white rats to lysis of the bacilli.

The possibility that subsequent inoculations may have been instrumental in clearing away beginning infection must not be forgotten—in addition to individual natural resistance—in the case of such guinea-pigs as No. 44.

The majority of our pigs weighed from 300 to 600 grams at the beginning of inoculations. Many, although becoming tuberculous, gained considerable weight.

The need for some form of vaccination against tuberculosis will probably always be felt, in spite of the 40 to 50 per cent. decrease in the death-rate in certain educated communities. Vaccination, applied fully and repeated once or twice in the age of greatest predisposition, has almost abolished smallpox whenever it has been tried. Nothing else has done this, and all localities fail that try to get along on sanitation alone.

The question of applying our procedure to man is to be approached with considerable care. Should he already have tuberculosis in any form, it is difficult to imagine that the addition of one bacillus to his probable millions could harm him, and yet even more difficult to imagine it could possibly do him any good. But should that unit begin to produce some immunity, especially a local immunity, the subsequent introduction of say five, and then perhaps multiples of five or less, might find the way prepared for their destruction and so general immunity might progress.

Perhaps the highest art to-day in the treatment of pulmonary tuberculosis consists in the control of the patient's inoculating himself, or auto-inoculation, resulting from exercise, elaborated by Paterson and Inman.[35]

Such auto-inoculations must result in the discharging into the lymph- and blood-channels from the foci of disease not only toxins, but in all probability live bacilli. It would be of great interest to make a study of blood cultures before and after such exercise. We have ourselves observed in similarly exercised patients changes resulting in their opsonic indices of greater extent than we have found produced by the inoculation of tuberculin. F. Klemperer inoculated tuberculous patients with cultures of virulent bovine bacilli.[36] Moeller inoculated tuberculous patients with a culture of human bacilli, modified by passage through the crocodile.[37] Every one knows that a local suppurative tuberculosis occurring in a consumptive improves his condition and increases his resistance.

We have inoculated five tuberculous men. The inoculations have always been made in the leg, arm, or forearm in such a manner that each new injection was received just below the former. The reason for this is that, should any local immunity be established, the new bacilli would perish more readily passing through such an area.

Case I: Catarrhal tuberculosis, involving a large part of the left lung and the apex of the right lung. No expectoration or cough. Frequent clearing of larynx. Moro inunction test negative. Negative from *x*-ray confirmatory of physical findings.

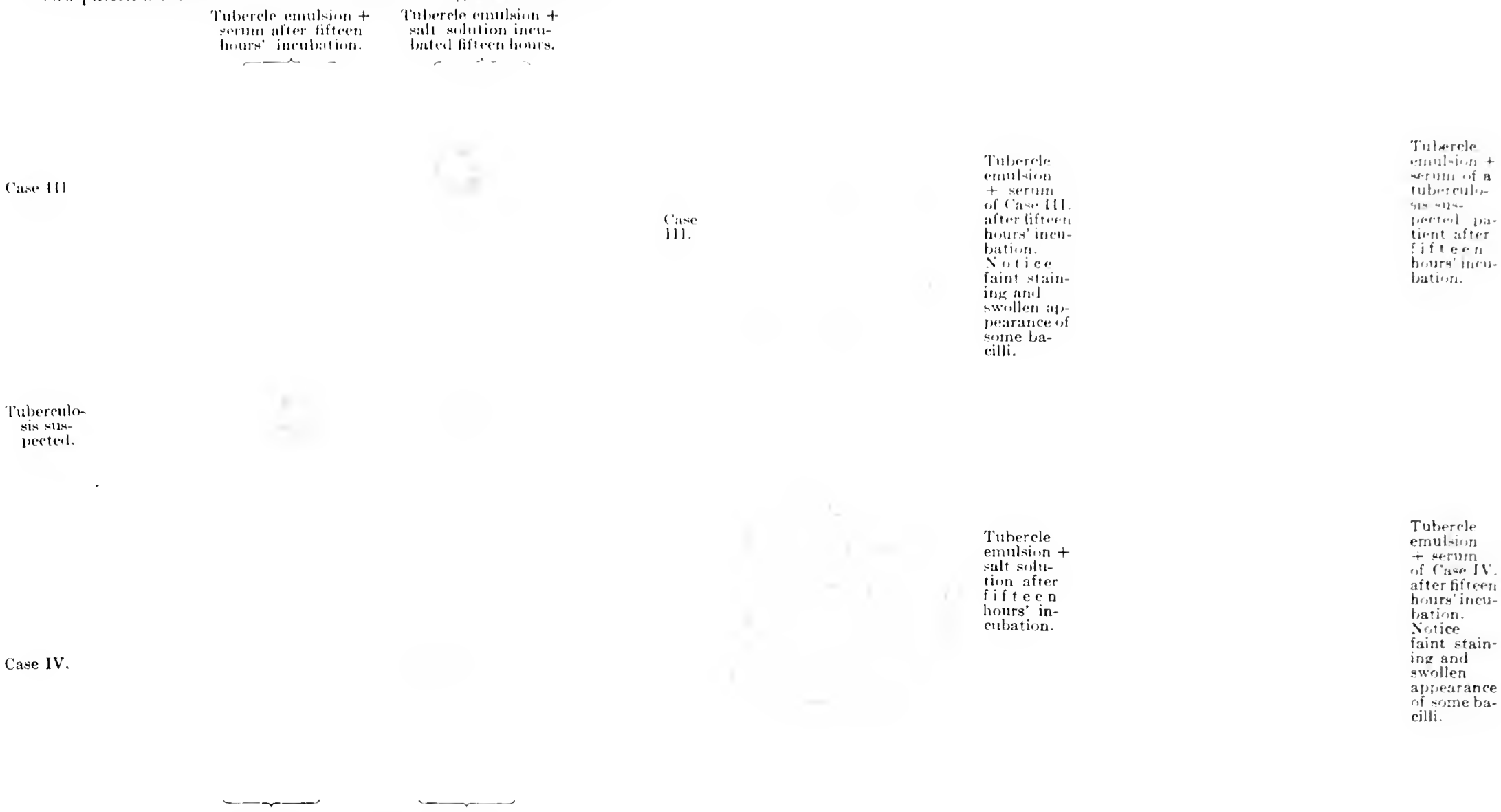
Dose: One tubercle bacillus, culture (B). Sixty days later no trace whatever of inoculation site.

Case II: Catarrhal tuberculosis. Both apices. No expectoration or cough. Frequent clearing of larynx. Moro reaction positive. Fluctuating opsonic index to tubercle. Negatives from *x*-ray confirmatory of physical findings.

Dose: One tubercle bacillus (B) followed by five tubercle bacilli after six days. Sixty days later no evidences of either site of inoculation.

Case III: Extensive pulmonary tuberculosis. Turban Stadium, III. Persistent fever one year, 99° to 100° F. Tuberculin treatment three months without results. Sanatorium treatment without results. Patient confined absolutely to rest at home without improvement. First inoculation one tubercle bacillus (Culture B). Subsequent inoculations at intervals of

two patients treated with inoculations of living tubercle bacilli.



These drops were placed on the slides after fifteen hours' incubation of a homogeneous emulsion of tubercle bacilli, with equal portions of serum or of salt solution. The staining was applied simultaneously according to the Ziehl-Neelsen method.

four to seven days: 5, 12, 20, 50, 100, 150, 150, 200, 250, 300, 350, 400, 450, 500, 500, 500. Following the ninth dose the temperature fell to and remained normal, and has been normal ever since. Patient is now up and walking, and comes to the laboratory for inoculation. There has been no reaction of any kind, local or general. Patient is amazed and delighted at his improvement. Tubercle bacilli are still present in the sputum. Physical examinations reveal a very much drier condition of his chest and markedly less sputum is raised. It is unfortunate that the opsonic index was not studied before inoculation. Following the eighth dose it was 1.23; following the tenth, 1.44. An inoculation of 300 tubercle bacilli with index at 0.75, four days later the index became 1.04. Subsequent to the inoculation of 350 it has been 1.14; 1; 1.07; 1.13. Still under inoculation. General health excellent; process arrested.

Case IV: Acute pulmonary tuberculosis. Turban Stadium, II. First inoculation, 50 tubercle bacilli. Subsequent inoculations at intervals of four to seven days: 100, 150, 200, 250, 300, 350, 400, 450, 500, 500 bacilli.

Opsonic index before inoculation was started, 0.69. Following the dose of 250, 0.92. Four days later, 1.07. Seven days later, 0.6.

Subsequent observations have been 0.83; 1.26; 0.89; 0.98; 1.08.

Following the sixth inoculation all fever disappeared and cough was much improved. Weight was being gained. After seven weeks able to do light work.

January, 1909: Discharged cured after twelve further inoculations of 500 bacilli.

Case V: Dr. G. W. P. Extensive pulmonary tuberculosis. Ten years' duration. Turban Stadium, III.

Tuberculin treatment two years, sanatorium three years, without distinct benefit.

First inoculation, one tubercle bacillus. Subsequent inoculations at intervals of four to seven days: 5, 25, 125, 250, 475, 500, 500, 500, 500, 500 bacilli.

The opsonic index at the beginning was 0.87. Subsequent observations after four and seven days subsequent to inoculation have been: 1; 0.72; 9; 1; 1.05; 1.04; 0.88; 0.91; 1.07; 1.28.

Estimation of the degree of lysis according to the lytic index[41] was three times normal, following the first dose of 500.

Patient feels generally better, although he has once or twice experienced a feeling of languor following inoculations. General improvement cannot be demonstrated, although the doctor feels a decided general gain. No apparent harm has been done. There have been no reactions, local or general, and no lesions of any character at inoculation sites.

The chief interest of these cases lies in the fact that no harm has been done that can be recognized, after one hundred and fifty days (January 9, 1909); that remarkable benefit accrued in two cases considered hopeless, and this, with so few bacteria injected in proportion to what would be present in tuberculin therapy. From our work on guinea-pigs we feel that some immunity can be safely produced by beginning with the subcutaneous inoculation of one tubercle bacillus, and we regard such a method as

being harmless, and more than probably beneficial to an already tuberculous man.

REFERENCES.

1. Rabinowitsch, Lydia: Virchow's Archiv, cxc, Beiheft.
2. Hutyra: Zeitschrift für Tiermed., 1907, xi, 241.
3. Koch: Proceedings International Medical Congress, Berlin, 1890.
4. Koch: Deutsche med. Wochenschrift, No. 14, 1897.
5. Pearson: Proceedings of the First International Veterinary Congress of America, 1893.
6. Trudeau: Amer. Jour. Med. Sci., Aug., 1906; June, 1907.
7. Dixon: Medical News, Philadelphia, Oct. 19, 1889.
8. Trudeau: N. Y. Medical Journal, July 23, 1893.
9. Trudeau: Address before the Henry Phipps Institute. Medical News, Oct. 24, 1903.
10. Pearson: Second Annual Report, Henry Phipps Institute.
11. De Schweinitz: Medical News, Dec. 8, 1894.
12. McFadyean: Journal Compar. Pathology and Therap., June, 1901; March, 1902.
13. Levy, E.: Centralblatt für Bakt., 1903.
14. Pearson and Gilliland: Phila. Medical Journal, Nov. 29, 1902.
15. Von Behring: Beiträge zur experimentellen Therapie, Reft. s. Marburg, 1902.
16. Thomassen: Recuil de med. vet., Jan. 15, 1903.
17. Neufeld: Deutsche med. Wochenschrift, Sept. 1, 1902; April 28, 1904.
18. Pearson and Gilliland: University of Penna. Med. Bulletin, April, 1905.
19. Smith, Theobald: Journal of Medical Research, June, 1908.
20. Koch: Zeitschrift für Hygiene u. Infektions-Krankheiten, 1905, li, 300.
21. Wright, A. E.: Antityphoid Inoculation.
22. Ricketts: Infection, Immunity, and Serum Therapy.
23. Strong: The Protective Inoculation Against Plague, Journal of Medical Research, May, 1908.
24. Calmette: Annales de l'Institut Pasteur, 1907, xxi, 525.
25. Baumgarten: Berlin. klin. Wochenschrift, 1904, 1124.
26. Lignieres: International Vet. Cong., 1905, iii, 95.
27. Hutyra: Journal Experimental Medicine, 1898, iii, 451.
28. Smith, Theobald: Journal of Medical Research, June, 1908, 455.
29. Virchow's Archiv, 1890, cxix, 127.
30. Preyss: Münchener med. Wochenschrift, 1891, S. 418.
31. Findel: Zeitschrift für Hygiene und Infektions-Krankheiten, lvii, 1907.
32. Ziesché: Die Verbreitungsweise und Bekämpfung der Tuberkulose, 1897–98.
33. Adami: Principles of Pathology, 184.
34. Barber: The Kansas University Science Bulletin, iv, No. 1, March, 1907. On Heredity in Certain Microörganisms.
35. Paterson and Inman: Lancet, Jan. 25, 1908.
36. Klemperer, Felix: Zeitschrift für klinische Med., lvi, 258.
37. Moeller: (Verbal P. Calmette.)
38. Pearson and Gilliland: American Vet. Rev., N. Y., 1905–06, xxix, 272, 278.
39. Heymans: Arch. Internat. de Pharmacol., Bruxelles, 1905, xix, 171, 175.
40. Lannelongue: Influences modificatrices de l'évolution Tuberculeuse. Paris, 1908.
41. Webb: Illinois State Medical Journal, June, 1908.

Following this paper Professor M. A. Barber, of the University of Kansas, demonstrated his method of isolating single bacterial cells. Professor Barber demonstrated this procedure at several times and places during the Congress.

La Production de L'Immunité par L'Inoculation de Bactéries Aux Nombres Augmentants, en Commençant par un seul Organisme Vivant.—(WEBB, WILLIAMS, AND BARBER.)

1. *Historique.*—Les tentatives de produire l'immunité permanente contre la tuberculose, par les inoculations de bacilles tuberculeux morts ou leurs produits, n'ont pas été satisfaisantes.

Au contraire, les inoculations d'organismes attenués mais virulents donnent de meilleures évidences de l'acquisition d'une immunité vraie. Nous présentons comme exemple les résultats obtenus dans les bestiaux par les inoculations des bacilles vivants de varietés humaine et bovine.

2. *L'Importance de se Servir Virus Vivant.*—Un degré relative d'une immunité acquise contre la tuberculose est indiqué par ce fait que probablement 60% de toutes les autopsies faites sur l'homme révèlent des lésions guéries. Les analogies avec les autres maladies se montrent—par exemple la variole, la rage.

3. *Technique Expérimentale.*—Les organismes furent obtenus choisis de "gouttesus" (hanging drops) selon la technique de M. A. Barber. Les inoculations furent faites sous la peau.

4. *Les Expériences.*—(*a*) Souris avec bacilles de charbon: On donne en premier lieu un fil (environ 3 organismes), augmentant graduellement jusqu'à 500 fils sans causer aucune évidence de dérangement. L'immunité ainsi créée.

(*b*) Cobayes avec bacilles tuberculeux. La dose initiale d'un seul bacille est graduellement augmentée de plus de 10,000, sans évidence de tuberculose jusqu'à present. Les évidences de l'immunité.

(*c*) Lapins avec bacilles tuberculeux. Résultats de soumettre aux inoculations semblables à la précédente, des lapins préalablement rendus tuberculeux en leur donnant à manger des bacilles tuberculeux.

5. *Inoculations Semblables chez L'homme.*—Résultats.

Immunität hervorgerufen durch Inoculation anwachsender Mengen von Bakterien, beginnend mit einem lebenden Organismus; therapeutische Anwendung.—(WEBB, WILLIAMS, UND BARBER.)

1. *Historisches.*—Die Bestrebungen, eine andauernde Immunität hervorzurufen gegen Tuberkulose durch die Inoculation toter Tuberkelbazillen oder ihrer Produkte haben sich nicht als befriedigend erwiesen.

Andererseits hat die Inoculation von verdünnten und virulenten Organismen mehr Evidenz einer hervorgerufenen wahren Immunität gegeben. Zur Illustration: die bei Rindern erhaltenen Resultate durch die Inoculation lebender Bazillen des Human- und Bovintypus.

2. *Die Wichtigkeit, einen lebenden Virus zu verwenden.*—Ein relativer

Grad aquirierter Immunität kann durch die Tatsache angenommen werden, dass beiläufig 60% aller Autopsien bei Menschen geheilte Verletzungen zeigten. Analogien mit anderen Krankheiten, als Variola, Rabies, etc.

3. *Experimentelle Technik.*—Organismen von hängenden Tropfen ausgewählt nach der Technik von M. A. Barber. Subcutane Inoculationen.

4. *Experimente.*—(*a*) Mäuse mit Anthraxbazillen. Anfangsdosierung ein Faden (ungefähr 3 Organismen). Nach und nach ansteigend zu 500 Fäden ohne irgend eine Krankheitserscheinung zu zeigen. Immunität dadurch hervorgerufen.

(*b*) Meerschweinchen mit Tuberkelbazillen. Anfangsgabe ein Bazillus gradatim ansteigend bis über 10,000 ohne Symptome von Tuberkulose. Evidenz von Immunität.

(*c*) Kaninchen mit Tuberkelbazillen. Resultate der Behandlung von Kaninchen, die durch Fütterung mit Tuberkelbazillen tuberkulös gemacht worden waren, mit Inoculationen ähnlich den oben erwähnten.

5. *Ähnliche Inoculationen am Menschen.*—Resultate.

DISCUSSION.

Dr. Robert Koch.—The first claims for the possibility of obtaining a tuberculosis immunity in cattle were quite generally disputed, but it is now undoubted that such immunization of cattle is realizable. I find myself in complete accord with Dr. Calmette, of Lille, whose experiments have been repeated and fully confirmed by the Imperial Health Department at Berlin. These experiments of Dr. Calmette establish the following two points, which I indorse:

1. Reinoculation shows that a relative immunity is established in cattle, but of limited duration.

2. That cattle inoculated for this purpose of immunization with living tubercular germs retain such bacilli in a latent condition for somewhat long periods of time; but when this period of apparent immunity ends, the latent bacilli may burst into activity and cause a fatal result.

Because of these evidences of limited immunity and the menace of the latent bacilli in such treatment of the cattle, I do not know of any present practically possible immunization of cattle. It may be well to keep in suspense our hopes of such immunity for the human being for the near future. Efforts in this direction are received with skepticism, and in this spirit did I receive this new idea of Drs. Webb and Barber of inoculating a definite number of tubercle germs in an effort to use the limit of number, instead of attenuation of bacilli, for purpose of immunization. My skepticism was particularly aroused as to their ability to inject a single bacillus; but my

doubts, on this point at least, have been removed by my investigation of the very excellent and efficient technic of Dr. Barber.

Dr. Edward L. Trudeau.—In my earliest work my belief has always been that through the agency of the living tubercular bacilli alone could successful immunization be hoped for. An occurrence in my own work of this nature quite confirms the statements of Dr. Calmette:

I thought it might be possible to obtain a successful vaccinating matter from the tissue substance of immunized cattle, the immunization being there provoked by injection of living tubercular bacilli. A cow was so injected, and when immunized, was slaughtered. Tissues of this animal, apparently absolutely free from any abnormal reaction or any bacilli, were rubbed up, and the emulsion injected, to test its vaccine reaction. There was none. But every animal of the series of this experiment was infected with tuberculosis, thus showing the persistence of latent but virulent living bacilli in this immunized cow, confirming Calmette's position.

I wish to mention the persistence of the infective power of old cultures which I have noticed in the course of my work. A culture of my own, maintained by successive cultures for more than fourteen years, is still infective. It causes involvement of the glands, even generalizing to the point of involving the spleen, but never determines a fatal end of the experimental animals. In my work of vaccinating it appears that the greater the virulence of the initial germ, the stronger the resultant vaccination result. That is to say, a low virulence of the original germ gives vaccine producing the lesser degree of resistance to infection.

The experiments of Dr. Calmette showing that infection results from serial reinfection, and not from a single light infection, that cures of itself and establishes a period of immunity, would seem to be capable of practical application for human immunization.

The method of Drs. Webb and Barber is certainly novel, and the idea of immunizing by a definite number low of tubercle bacilli differs from the usual efforts for immunity by employing attenuated cultures.

My own work with small and very diluted doses of infecting germs is, of course, not so minute, but, as far as my results go, the promise in this line is not radiant.

Dr. M. J. Rosenau called attention to the American work on the hypersusceptibility.

The tuberculin reaction is manifestly of this nature, showing the hypersusceptibility of the animal of experiment. The ophthalmo-reaction of Calmette shows, by the rapidity and intensity of reaction, that the organism is in the best state of active resistance; the rapidly induced conjunctival reaction demonstrates the quick efforts of the tissues of such organism to limit and eradicate the invasion.

LES TUBERCULINES ET LA MESURE DE LEUR ACTIVITÉ.

Par M. le professeur A. Calmette,
Institut Pasteur de Lille.

Depuis que Robert Koch a préparé sa première tuberculine, aujourd'hui communément désignée sous le nom de vieille tuberculine (Alttuberkulin) ou de tuberculine brute, on s'est efforcé d'obtenir une substance plus pure et plus active au moyen de divers procédés.

La préparation initiale de Koch qui consiste en un simple extrait glycériné des cultures en bouillon stérilisées par chauffage, concentrées au bain-marie jusqu'à réduction au dixième du volume primitif et filtrées sur papier épais ou sur Berkefeld, présente l'inconvénient de contenir, outre les produits de sécrétion du bacille tuberculeux, une grande quantité de substances étrangères (albumoses, peptones, sels et glycérine), susceptibles à elles seules de provoquer une fièvre passagère lorsqu'on les injecte à des sujets non tuberculeux et de masquer ainsi les effets dûs à la tuberculine elle-même. Aussi Koch chercha-t-il bientôt à éviter cet inconvénient en recommandant l'emploi des tuberculines TO et TR obtenues par le broyage mécanique de bacilles secs dont il séparait ensuite, par l'eau légèrement alcalinisée, les produits solubles et insolubles.

D'autres auteurs, en particulier Klebs, Buchner et Hahn, Behring, Landman, and Béraneck, ont séparé des cultures, au moyen de divers traitements chimiques, des substances (tuberculocidine, tuberculo-plasmine, tuberculosine, etc.), assez différentes de la vielle tuberculine, et qui ne semblent pas posséder les mêmes propriétés physiologiques et thérapeutiques.

Pour respecter autant que possible les produits de sécrétion des bacilles, Denys et Buden (de Louvain), se bornent à utiliser les cultures filtrées au Chamberland, et Maragliano, de même que von Ruck, préfèrent employer simplement un extrait aqueux de bacilles, sans glycérine.

Tous ces efforts attestent l'intérêt que portent à la fois les bactériologistes et les cliniciens à l'obtention d'un produit qui réunisse les avantages de la vieille tuberculine de Koch et qui écarte les inconvenients présentés par celle-ci du fait du trop grand nombre d'impuretés qu'elle renferme.

À la suite de nombreux essais j'ai été conduit à préparer pour l'usage thérapeutique une tuberculine particulièrement active et relativement très-

pure, dite tuberculine CL, qu'on peut introduire dans l'organisme des animaux sains, même à haute dose et par voie intraveineuse sans provoquer d'élévation de température, ce qui est tout-à-fait impossible avec les autres tuberculines. On peut en injecter impunément 50 centigrammes en une seule dose dans la veine jugulaire d'un bovidé sain: il n'en résulte aucune réaction. Par contre si la même injection, à la même dose, est répétée trois fois à 6 ou 10 jours d'intervalle, on constate que 5 à 12 heures après la troisième injection l'animal réagit de 1° 8 à 2° 5, comme s'il était tuberculeux et, chose plus intéressante encore, il est rendu manifestement très résistant aux infections tuberculeuses artificielles: si l'on vient à lui injecter dans les veines une dose de bacilles tuberculeux bovins virulents capable de donner sûrement une tuberculose miliaire aigüe mortelle en 4 à 6 semaines aux animaux témoins-l'animal préparé par les injections préalables de tuberculine ne prend qu'une tuberculose chronique à évolution très lente.

La tuberculine dont il s'agit est obtenue en concentrant dans le vide à froid les cultures entières de tuberculose bovine. Le produit est ensuite filtré pour séparer les corps microbiens, précipité à trois reprises différentes par l'alcool-éther, repris par l'eau et dialysé jusqu'à élimination complète des peptones et des sels. Les substances colloïdes qui restent sur le dialyseur sont finalement précipitées une dernière fois par l'alcool-éther et desséchées dans le vide.

Aucun chauffage et aucun traitement chimique autre que les précipitations par l'alcool-éther ne viennent ainsi modifier la substance active et celle-ci peut alors être titrée par comparaison avec les autres tuberculines et avec une grande précision, grâce à la méthode d'inoculation directe dans le cerveau du cobaye sain, préconisée déjà par von Lingelsheim. On constate ainsi que .0008 dixièmes de milligr. de cette tuberculine CL suffisent à tuer le cobaye sain, tandis qu'il faut au moins dix fois plus du précipité alcoolique de l'ancienne tuberculine de Koch, soit 0 gr. .008 pour obtenir le même résultat.

Cette tuberculine CL est très-bien supportée par les malades tuberculeux. Les médecins qui l'ont expérimentée, soit dans les hôpitaux, soit dans les sanatoriums, suivant mes indications, en ont obtenu d'excellents effets. Pas plus que les autres tuberculines elle ne guérit la tuberculose, mais elle retarde manifestement l'évolution de celle-ci et confère à l'organisme une résistance évidente à l'infection.

Pour en obtenir les meilleurs résultats, on doit l'employer à doses très-faibles d'abord, à partir de 1 millième de milligramme, et on augment graduellement par fractions de 1 à 3 millièmes, centièmes et dixièmes de milligramme, en espaçant les injections à intervalles de 10 à 12 jours, afin d'éviter rigoureusement toute réaction thermique supérieure à un demi-degré centigrade, et en s'attachant à maintenir l'index opsonique constam-

ment plus élevé ou égal à ce qu'il était lors de l'injection précédente. La mesure de l'index opsonique des malades permet en effet, comme l'a montré Wright, de suivre exactement l'évolution ascendante du processus de défense de l'organisme.

L'étude expérimentale de la tuberculine préparée comme je l'ai indiqué ci-dessus montre que cette substance possède *in vitro* une affinité évidente pour les lipoïdes (probablement identifiables à la lécithine) que renferment presque constamment les sérums d'hommes et de bovidés tuberculeux. J'ai exposé dans d'autres travaux l'importance de cette réaction qu'on peut déceler grâce à l'activation du venin de cobra par la* lécithine libre des sérums. Il est donc tout à fait indiqué de l'utiliser, non seulement pour le diagnostic des différentes formes de tuberculose, mais aussi pour la détermination de l'affinité du sérum des malades à l'égard des produits de sécrétion du bacille tuberculeux.

Son emploi méthodique permettrait certainement aux cliniciens de se rendre un compte exact des effets de la médication tuberculinique, ce qui leur était fort difficile ou même impossible jusqu'à ces derniers temps.

Tuberculins and the Measure of Their Activity.—(CALMETTE.)

Since Robert Koch prepared his first tuberculin, efforts have been made by means of various processes to obtain a purer and more active substance. Koch's old tuberculin unfortunately contains, besides the secretory products of the tubercle bacilli, a large quantity of foreign substances which are capable of producing a temporary rise of temperature when injected in non-tuberculous subjects, and thus masking the effects due to the tuberculin itself. Before long Koch himself tried to overcome this defect by advising the use of the tuberculins TO and TR obtained by mechanically crushing the dried bacilli and then separating by means of slightly alkaline water the soluble and insoluble products. Other authors, by means of various chemical products, isolated from the cultures a variety of substances which are quite different from the old tuberculin and do not appear to possess the same physiological and therapeutical properties. In order to preserve as far as possible the secretory products of the bacilli, Denys and Buden confined themselves to cultures filtered through a Chamberland, while Maragliano and von Ruck preferably employed a simple aqueous extract of bacilli without glycerin. These various attempts all tend to show a great desire on the part of pathologists and clinicians to obtain a product which would possess all the advantages of Koch's old tuberculin without producing the disturbing effects due to the large number of impurities which it contains.

* C. R. Académie des sciences, 30 mars et 25 mai, 1908.

After numerous experiments I finally prepared an active and relatively pure tuberculin called tuberculin CL, which can be introduced intravenously into the body of a healthy animal in large doses without producing any elevation of temperature. As much as 50 centigrams may be injected into the jugular vein of a healthy animal of the bovine species without producing any reaction; on the other hand, if the same injection is repeated three times, at intervals of six to ten days, the animal is observed, in from five to twelve hours after the third injection, to react by a rise of 1.8 to 2.5 degrees of temperature, just as if it were tuberculous; and what is more interesting, the animal acquires a high degree of resistance to artificial tuberculous infections. The intravenous injection of a dose of virulent bovine tubercle bacilli (sufficient to produce an acute fatal miliary tuberculosis in control animals) merely produces a chronic and slowly progressing tuberculosis. This tuberculin is obtained by centrifugating in vacuo, and at a lower temperature, entire cultures of the bovine bacillus. The product is then filtered, precipitated three times with alcohol and ether, redissolved in water, and dialyzed until all the precipitants and salts have been completely eliminated. The colloid substances which remain on the dialyzer are then precipitated once more with alcohol and ether and dried in vacuo. Hence the active substance is not modified by heat or any chemical treatment except precipitation with alcohol and ether, and its activity can then be determined by comparing it with the other tuberculins, or with a high degree of accuracy, by the method of direct inoculation into the brain of a healthy guinea-pig. It is thus found that 0.0008 milligram of this tuberculin CL suffices to kill a healthy guinea-pig, whereas almost ten times as much of the alcoholic precipitate of Koch's old tuberculin, or 0.008 gm., is required to produce the same result. This tuberculin CL is very well borne by tuberculous patients. Physicians who have experimented with it according to my directions have obtained excellent results. It does not cure tuberculosis any more than any other tuberculin, but it evidently delays the progress of the disease and endows the organism with resistance to the infection.

In order to obtain the best results with tuberculin CL very small doses, $\frac{1}{1000}$ milligram, should be employed at first, and the dose gradually increased by fractions of one to three thousandths, hundredths, and tenths of a milligram—administering the injections at intervals of ten to twelve days, in order to avoid a reaction of more than one-half degree Centigrade. At the same time an effort should be made to maintain a constant increase of the opsonic index over the index of the previous injection, or at least to maintain it at the same level. By measuring the patient's opsonic index it is possible, as Wright has

shown, to follow accurately the gradual rise of the defensive processes of the organism.

An experimental study of tuberculin prepared according to the above directions shows that the substance in vitro possesses an affinity for the lipoids (probably identical with lecithin), which are almost constantly contained in the serum of tuberculous human beings and cattle. Elsewhere I have shown the importance of this reaction, which can be demonstrated by utilizing the fact that cobra-venom is rendered active by the free lecithin of sera; hence the tuberculin is clearly indicated not only for the diagnosis of the different forms of tuberculosis, but also for determining the affinity of the patient's serum for the secretory products of the tubercle bacilli.

Its systematic employment enables the clinician to observe the effects of tuberculin medication accurately—a thing which until recently has been exceedingly difficult or impossible.

THE TREATMENT OF PULMONARY TUBERCULOSIS WITH TUBERCULINUM PURUM.

By Dr. J. Gabrilowitch,
Physician-in-Chief at the Imperial Sanatorium at Halila, Finland.

Tuberculinum purum contains in full measure the active principles of Koch's old tuberculin. It is prepared from cultures of tubercle bacilli of the human variety, but is so altered by means of chemical reagents that, when used subcutaneously, it produces no general reaction. This tuberculin can be used in large and rapidly increasing doses, both in children and adults. It acts upon the lung itself, as shown by the fact that it causes the catarrhal symptoms to disappear, and the lung may be said to "dry out" under its influence. In cases with circumscribed pulmonary lesions, from 16 to 20 injections were found sufficient; in cases in which larger areas of lung were involved, or in which an entire lobe was affected, or in cases with disseminated foci, from 50 to 60 injections have been found necessary.

The process of repair under the influence of tuberculinum purum may be clearly followed clinically. Often one gains the impression that a temporary aggravation of the local process takes place at first. The catarrhal symptoms become more pronounced and the number of bacilli increases in the expectoration. The diminished or roughened respiratory murmur becomes bronchial in character; the bronchial breathing becomes amphoric. But these symptoms disappear rapidly, and the lung grows clear. During the treatment the general condition of the patient remains always good; there is no loss of weight, and the temperature falls to normal.

Tuberculinum purum can also be used in cases of acute or subacute tuberculosis. Tuberculinum purum is not contraindicated in the presence of complications in organs other than the lungs. The most favorable results have been in chronic, uncomplicated cases. The use of the remedy is not followed by unpleasant subjective or objective symptoms.

One-third of the 25 cases treated by the author with tuberculinum purum belonged to the severe types of cases, and only 12 per cent. could be classed as mild cases.

The tubercle bacilli disappeared from the expectorations in 59 per cent. of the cases; the bacilli diminished considerably in number in 31 per cent.

The catarrhal symptoms in the lungs disappeared in 75 per cent., and were lessened in 25 per cent. The temperature became normal during treatment in 31 per cent., and at the completion of treatment in 62 per cent.

The number of injections was 20 in 80 per cent. of the cases. The duration of treatment was from forty to sixty days. The initial dose was almost uniformly 0.01 milligram, while the terminal dose was from 100 to 200 milligrams.

The patients gained in weight in 96 per cent. of the cases, the gain ranging from 1 to 6 kilos. As a diagnostic measure, tuberculinum purum may be used in doses of 0.5 milligram. In undiluted form it produces von Pirquet's cutaneous reaction in the presence of tuberculosis.

Tratamiento por Medio del Tuberculinum Purum.—(Gabrilowitch.)

El tuberculinum purum contiene en un todo los principios activos que se encuentran en la antigua tuberculina de Koch. Está preparado de cultivos de bacilos tuberculosos de la variedad humana. En caso de lesiones pulmonares circunscritas, se vió que eran suficientes de 16 á 20 inyecciones; en casos en que estaban comprometidas porciones mayores del pulmón, ó cuando se trataba de estar afectado todo un lóbulo, ó bien en casos de focos diseminados, se ha visto que eran necesarias de 50 á 60 inyecciones. El proceso de restauración bajo la influencia del tuberculinum purum, puede seguirse clínicamente. Con frecuencia se produce en el ánimo la impresión de que lo primero que ocurre es una agravación temporal del proceso local. Los síntomas catarrales se hacen mas pronunciados, y en la expectoración aumenta el número de bacilos. Pero estos síntomas desaparecen con la misma rapidez que se producen y el pulmón se va despejando. Durante el tratamiento, el estado general del paciente es siempre satisfactorio; no hay pérdida de peso y la temperatura desciende hasta la normal. El autor da usado el tuberculinum purum tanto en el Sanatorio como en la práctica particular de su profesión, y siempre ha dado buenos resultados. De los 25 casos tratados por el autor con tuberculinum purum, una tercera parte pertenecían á casos típicos graves y sólo el 12% podían considerarse como casos sin importancia. La dosis primera fué casi con una uniformidad de 0.01 miligramos, mientras que la dosis final fué de 100 á 200 miligramos. Los pacientes aumentaron de peso en el 96% de los casos, llegando á ser este aumento de 1 á 6 kilos. La gran ventaja del tuberculinum purum radica en el hecho de que puede usarse con facilidad en el ejercicio particular de la profesión, porque no hay que temer con el uso señales de reacción inesperadas.

EUPYREXIA.

By Camilo Calleja, M.D.,
Madrid.

The aim of this clinical study is to increase our knowledge, as yet slight, regarding pretuberculosis, with which natural immunity comes into such close relation.

I call this pretuberculous fever "eupyrexia," this word meaning good fever, by antonomasia, that is, the best of all fevers, a disease almost exclusively belonging to youth and children. The inquiry into this affection is very interesting, since it gives us a clear account of the generation of tuberculosis, and also because it is the base upon which we establish the scientific principles regarding the prophylaxis of this disease.

This is an infection in which we must consider accurately the two factors: the internal, that is, the state of the constitutive cells of the body, and the external, the medium in which the cells live. In regard to the eupyrexia, the two factors are: (1) a deficiency of the constitutive oxygen of the cells of the body; this deficiency I denominate hypoxygenia; and (2) a superabundant proliferation in the body of the saprophytic tuberculous bacteria, which I call Ferran's bacilli.

Hypoxygenia, that is, the lack of reoxygenation in the organism, may be either primary or secondary. Primary hypoxygenia is a general asthenia due to imperfect breathing and an insufficient intake of oxygen, so that there is an imperfect compensation of the oxygen we constantly lose. Secondary hypoxygenia may be either general or local; the former is at times caused by chronic infections like lues, or chronic intoxications like alcoholism, sometimes by primary anemia resulting from poor alimentation; and also it may be produced by a dyscrasia, especially when the individuals are narrow-chested (dolichosomatous). Local hypoxygenia may be produced by traumatism and also by an idiosyncrasy; this is generally inherited from ancestors suffering from sclerotic diseases, among which nicotinism, besides the disease before mentioned, is one of the most important. In secondary hypoxygenia, the want of oxygen in the system is the result of the tissues having lost some of their power of reoxygenation on account of their presclerotic state. Complex hypoxygenia is that in which the primary and secondary forms are combined in the same subject.

Sufferers from chronic hypoxygenia are predisposed to pretuberculous

affections, one of which is eupyrexia; but germs are indispensable to the development of tuberculosis. These germs, which are Ferran's bacilli, are non-acid-fast, are somewhat similar to the B. coli communis, and can be transformed into Koch's bacilli and vice versâ. Besides, they determine by inoculation tuberculous processes. As Koch's bacilli can scarcely live outside the pathological tissues or in places exposed to air and sunlight, while Ferran's bacilli are almost everywhere, to these we must impute the beginning of pretuberculosis and consequently of eupyrexia.

Once Ferran's bacilli invade the tissues they produce an infection, which, like all infections, is a real fecundation (and not merely the sowing of a seed, as is generally believed). The pretuberculous infection begins by nervous alterations; then, if the stimulus of Ferran's germs continues, hyperemia is determined; afterward the congestion, instead of remaining local, may become general, and pretuberculous fever or eupyrexia is produced. In addition to this the local process may advance further, developing into an inflammatory process, and later on special granulations—which I call euphymia (that is, good growth)—may be formed. To sum up, there are five degrees of pretuberculous affections: neuroses, hyperemias, fevers, inflammations, and granulations. Moreover, there are complex pretuberculous affections in which two or more of the elemental ones, which I have just mentioned, are united. To understand what is pretuberculosis, and the place euphymia has in the process, we have to consider that the five different affections we have mentioned are like five correlative degrees of the same process, and that every one of the first four pretuberculous affections may either prevent or cure the following ones. That is to say, pretuberculous neuroses, hyperemias, fevers, and inflammations may be preventive processes of the pretuberculous granulations, and may be their curative process once they have appeared. For this reason the first four pretuberculous affections I call "antiphymias"; the eupyrexia being an antiphymic fever capable of preventing or of curing pretuberculous granulations, and even phymatosis really tuberculous, that is, having already Koch's bacilli. Again, Ferran's bacilli, by provoking pretuberculosis, are usually the natural cure for hypoxygenia, but in case of the latter being too intense, and the tissue being greatly degenerated, instead of hypoxygenia being resolved, the process becomes tuberculosis properly so called, because the degenerated tissues feed Ferran's bacilli with noxious products which change them into Koch's bacilli. We consider true tuberculosis only that condition in which we find both tuberculous tissues and Koch's bacilli.

Eupyrexia is a very important and frequent disease, especially in young people, and is manifest in different forms, but the principal may be reduced to four: (1) Pseudotyphic eupyrexia, which is the most typical. Belonging to this variety are many of the cases hitherto diagnosed as intestinal infections,

without specifying the cause; also many other fevers qualified as attenuated typhoids, and a great number of catarrhs of the digestive organs considered as grippal. (2) Pseudorheumatic eupyrexia, to which belong many of the cases generally qualified as rheumatic fevers, since, in my opinion, young people who are growing rapidly, when they suffer from long and irregular fever with pains in their limbs, without noticeable local swelling, generally suffer from eupyrexia. (3) Pseudopneumonic eupyrexia, which is marked by symptoms of congestion of the respiratory organs, like bronchitis, transitory pneumonia, and, when it lasts long, sometimes has the appearance of an incipient consumption. (4) Pseudopaludic eupyrexia, to which belong almost all paroxysmal fevers which are not malarial and are neither septic nor pyemic. I will add a few details regarding the diagnosis of the typical or pseudotyphic variety, which generally begins with one or more ephemeral pyrexial attacks similar to those produced by moderate malaria; then follows a remittent fever, increasing gradually like typhoid, but the general state of the patient, even after many weeks, does not present the characteristic symptoms of typhoid, this being the principal difference, that in euphymia the patients have neither the appearance nor the feeling of being ill.

With this and the antecedents, we can often reach a differential diagnosis; but it is not infrequent to see cases which are not diagnosed until a long time after having been cured, and the diagnosis is then established by some other pretuberculous or tuberculous manifestations presenting themselves. Surely, before long, with the advance of serum-diagnosis, with the establishment of the opsonic index, and other similar tests, we shall be able to recognize pretuberculosis from its beginning.

In pretuberculosis, as in all pathological processes, we must differentiate the bad effect of the causes of the disease from the good vital reaction of the organism. Regarding eupyrexia, hypoxygenia is the bad process, while the fever or general reaction provoked by Ferran's bacilli is the eubiotic or curative process. Unless this distinction be clearly understood, one will fall into the error of attacking every symptom the patient presents; and from the failure of the practitioner to make this distinction arises the frequent abuse of sedative therapeutics in neuroses, hyperemia, fever, inflammation, and new growths, although all these are nothing but the different degrees of the curative process. Eupyrexia in particular produces most beneficial results. Hence we must respect the fever, considering all antithermics contraindicated. We must further consider that, as Ferran's bacilli are the stimulants of vital reaction in pretuberculosis, we must not attack such germs, because, then, we unarm nature of her most valuable therapeutical resource.

The only efficacious treatment is to combat hypoxygenia, our efforts being directed especially to its prevention. The method must be different according to whether the hypoxygenia is primary, secondary, or complex.

For all alike, pure air is the best treatment, but the results are very different, being more marked in primary hypoxygenia.

Besides the chief indication, there are some vital ones, like those which arise from collapse and hemorrhages, which are to be treated as in any other disease. We must say the same regarding the repair of loss of substance and the restoration of the strength of the patient; nevertheless it is well to advise not to follow the old saying, "starve a fever"; on the contrary, when the first week of the fever has passed (during which it will be well to restrict the diet somewhat), we must give as much and as nutritious food as the patient can digest, so that the calories which the fever consumes may be made up. But it often happens that the digestive organs cannot do as much work as is necessary; then we must prescribe some preparations to help the metabolism, so that the bacilli become less virulent and the sufferer may resist the disease. For this purpose we may prescribe the phenol derivatives, the arsenicals, one of the colloidal forms of silver, and organic preparations such as tuberculin, always taking care to use them in small doses, as in eupyrexia they merely produce a stimulating effect upon the cells.

We must keep in mind that there is not, nor ever will be, a specific against eupyrexia; that the remedies proposed, and all those that may be recommended in the future, will be no more than palliatives, and that we must only employ resources which favor the vitality of the cells, without attacking Ferran's bacilli.

Spain offers to the pretubercuIous the most favorable climates to be found anywhere. In summer, on heights like Panticosa and seaside places like La Toga; and in winter, the mountains around Malaga, Almeria, and Alicante.

The definite prognosis of eupyrexia, that is, that judgment regarding the results of treatment, confirms, at least for the present, our assertion as to the limited influence of the therapeutical means at our disposal. The prognosis is uncertain, since the fever is seldom influenced by medical treatment. I do not pretend to have done more in attending eupyretic patients than to increase their resisting powers.

In conclusion: Our first aim in eupyrexia must be to prevent hypoxygenia, but once this is produced, eupyrexia is its best natural or spontaneous curative process. Hence we must help the development of eupyrexia in those suffering from hypoxygenia, for which pure air is the best recourse. Whether he breathes or does not breathe sufficient pure air may determine whether the individual suffers from eupyrexia or from consumption. Consequently, in addition to the direct preventive influence of atmospheric air, recognized by all as a means against tuberculosis, we have described here another preventive effect which, although indirect, is of great value, and is

exercised by means of the pretuberculous process which I denominate eupyrexia. This knowledge regarding eupyrexia gives rise to an optimistic conception of pretuberculosis, since, in my opinion, most cases of pretuberculosis, chiefly the eupyrexias, are substitutive processes, which act favorably on asthenic states, thus preventing the danger of cachexia and producing this natural immunity.

Eupirexis ó Fiebres Antifímicas.—(CALLEJA.)

I. Descripcion clínica de las Eupirexias: curso, duracion y terminacion. Un caso típico de la forma pseudotifoidea, y breves consideraciones sobre las variedades pseudo-pneumónica, pseudoreumàtica y pseudo-palúdica.

II. Etiologia de las tuberculosis en general y de las Eupirexis en particular: predisposicion y virus.

III. Patogenia de las tuberculosis en general, y de las Eupirexis en particular

IV. Juicios clínicos (Iatrocritica) de las Eupirexis: comentarios del diagnostico, del pronostico y del tratamiento.

V. Conclusion: proposiciones recopilando sumariadamente las ideas más importantes sobre las Eupirexis.

SECTION I.

Pathology and Bacteriology (*Continued*).

FOURTH DAY. AFTERNOON SESSION

Thursday Afternoon, October 1, 1908.

PROTEINS OF THE TUBERCLE BACILLUS. IMMUNIZING SUBSTANCES. ENZYMES. CHEMICAL STUDIES.

The Section was called to order by the President, Dr. William H. Welch, at half-past two o'clock.

A STUDY OF THE PROTEINS OF THE TUBERCLE BACILLUS.

By Victor C. Vaughan,

Ann Arbor, Michigan.

The Organism.—The tubercle bacillus with which this work has been done is one that has been grown on artificial culture-media for many years, and has lost its virulence for rabbits and guinea-pigs. This has been repeatedly demonstrated during the past eight or ten years, but in order to have renewed evidence, we inoculated four rabbits and five guinea-pigs intra-abdominally with the glycerin beef-tea culture, and these animals, having been killed from three to six months after inoculation, have in no instance shown evidence of infection. This bacillus has been grown on glycerin beef-tea at 37° and harvested after one month.

The Cellular Substance.—The growth is collected on hard filters and thoroughly extracted, first with absolute alcohol and then with ether, in large soxhlets. The alcoholic and ethereal extracts contain fats and waxes which will not be discussed in this paper. The cellular substance is then rubbed up and passed through a fine-meshed sieve. This forms a fine powder, which, under the microscope, reveals the individual bacilli. The tubercle protein, as thus obtained, takes the carbolic stain, but is no longer acid-fast.

Effect of the Cellular Substance on Animals.—Many guinea-pigs and rabbits have been treated intra-abdominally with from 5 to 200 milligrams of this substance, and the following statements may be made as to the results of these injections:

(1) In no instance was death caused directly by the injection. One pig died six days after receiving 20 milligrams. There were several caseous nodules in the omentum and one on the under surface of the liver. Microscopical examination showed that these nodules consisted of masses of leukocytes and the débris of the injected bacilli. One pig that received 5 milligrams was found dead nine days later, but careful search failed to reveal any traces of effects of the injection. Rabbits and guinea-pigs that received from 100 to 200 milligrams remained apparently well for months, and when killed, generally showed nodules at the point of injection and in the omentum. It follows from this that the dead cellular protein of the tubercle bacillus causes only a local effect.

(2) The cellular substance gives no immunity to subsequent inoculations with the living virulent tubercle bacillus. At least this is true with the material employed in these experiments. Six pigs that had received single intra-abdominal injections of the cellular protein, in amounts varying from 15 to 200 milligrams, were inoculated one month later with a virulent culture, and all developed tuberculosis and died from it within from nineteen to one hundred days.

(3) The cellular protein does, for a time at least, and in an imperfect manner, sensitize guinea-pigs to the Bacillus tuberculosis. This is an interesting point, and the only one which seems to me to hold out any hope of finding in the bacillus or among its split products a substance that might be beneficially employed in the treatment of tuberculosis in man. The following is an illustration of this action: Pig No. 159, weight 530 grams, received, December 18, 1906, 25 milligrams of the cellular protein intra-abdominally. Thirteen days later it was given by the same avenue a large loop of the avirulent culture suspended in salt solution. The animal was sick within a few minutes, manifesting the symptoms of protein poisoning. Within forty-five minutes the rectal temperature had fallen to 96° F., and the next morning the animal was dead. Autopsy showed a hemorrhagic peritonitis. I infer that the cellular protein sensitized this animal, and that the bacilli of the culture were broken up so rapidly, and their poisonous constituents set free so speedily, that the animal was killed. If this interpretation be correct, there remains at least the possibility that there may be found in the bacillary substance some constituent that may stimulate the cells of the animal body to split up and destroy tubercle bacilli. The cellular protein itself sensitizes only locally and imperfectly because of its insolubility.

The Protein Character of the Cell Substance.—That the cellular

substance of the tubercle bacillus is a glyconucleoprotein has been shown by work in my laboratory: (1) It gives all the protein color reactions; it contains a carbohydrate; it yields certain nuclein bases, as xanthin; it contains both mono-amino-acids and diamino-acids. In his studies of the mono-amino-acids my assistant, Agnew, has not only shown that the cellular substance of the tubercle bacillus is a protein, or a mixture of proteins, but that it is a protein *sui generis*, and that it differs radically from the protein of the colon bacillus. This is shown in the following table, in which the amounts of the mono-amino-acids found in the two are given:

	Colon Protein.	Tubercle Protein.
Glutamic acid	3.00 per cent.	0.22 per cent.
Glycocoll	0.33 " "	0.00 " "
Alanin	1.00 " "	1.57 " "
Valin	1.60 " "	5.17 " "
Leucin	2.00 " "	2.04 " "
Phenylalanin	0.20 " "	0.56 " "

Cleavage of the Tubercle Protein.—When the cellular protein of the tubercle bacillus is heated under a reflux condenser with from 15 to 25 times its weight of a 2 per cent. solution of sodium hydroxid in absolute alcohol, it is broken up into a poisonous and a non-poisonous, or a toxophore and a haptophore, portion. The former is soluble and the latter insoluble in absolute alcohol. The haptophore contains all the phosphorus and all the carbohydrate of the original cellular proteid. The toxophore consists largely of mono-amino-acids and diamino-acids, but the identification of these acids has not yet been made. In the haptophore the following mono-amino-acids have been obtained by Agnew in crystalline form: leucin, 1.76 per cent.; alanin, 1.10; valin, 0.63; phenylalanin, 0.46.

The Action of the Toxophore on Animals.—This, like all the similar bodies that we have obtained from bacterial, vegetable, and animal proteins, is a respiratory poison. It develops the three stages of peripheral irritation, partial paralysis, and terminal convulsions. When given in doses of 100 milligrams, it kills both healthy and tuberculous animals within an hour. When given to normal animals in much smaller repeated doses, it has no visible effect. In larger repeated doses in healthy animals it causes a condition of chronic intoxication, with loss in weight and general marasmus. When given, even in very small, repeated doses to tuberculous animals, it intensifies the tubercular process, and in all cases the treated animals die before the controls. All attempts to produce an antitoxin with it have failed.

The Action of the Haptophore on Animals.—This substance sensitizes animals to the unbroken cellular protein or to either the living or the dead bacillus. The haptophore sensitizes much more promptly and efficiently than the unbroken protein, because of its ready solubility. Single

doses of the haptophore up to 500 milligrams have been injected subcutaneously in tuberculous patients without any apparent ill effect. In some an elevation of temperature of from one to four degrees has, in many instances, but not invariably, followed the larger injections. I have used tubercle protein in the treatment of about 50 cases of pulmonary tuberculosis, and it has been used in a smaller number of cases of surgical tuberculosis. The results obtained in the surgical cases were reported at the last meeting of the Michigan State Medical Society by Dr. J. W. Vaughan, in a paper not yet published. I first used this preparation in 1905, and although I believe it to be preferable to any form of tuberculin, I am convinced that, like tuberculin, it is capable of doing harm. I am now using doses of from 1 to 10 milligrams at intervals of from one to two weeks. That these doses do profoundly affect the body is shown by the fact that if, after they have been continued for some weeks, the interval between two injections be increased to six weeks or longer, the next injection is likely to be followed by those alarming symptoms which we now regard as characteristic of the so-called serum disease. In other words, the haptophore of the tubercle protein sensitizes the human body, as well as the guinea-pig. Whether the injections should be continued in greatly reduced doses after this condition of sensitization has been reached or not I am not sure, but my experience leads me to believe that it should.

The haptophore of the tubercle protein as it has been prepared in my laboratory is tuberculin, or the tubercle protein with its poisonous group removed; at least this is my conception of it. It seems to me that recent studies on protein susceptibility and immunity, incorrectly designated as anaphylaxis, furnish some suggestive information concerning the genesis of tuberculosis. The tubercle bacillus is a living protein which, for countless generations, has infected man. Practically it has become an obligate parasite. Although it may retain its vitality when ejected from the animal body, under natural conditions it does not multiply until it finds lodgment in another host. Like all obligate parasites, it grows slowly in the host, because its continued existence is dependent upon the life of the host. It protects itself against the cells of the body and their proteolytic enzymes by coating itself, as it were, in fats and waxes. The bacilli that die in the tubercular nidus in the host undergo autolytic cleavage slowly, and the extent to which the body-cells are sensitized is at first quite limited. Sensitization to or against the tubercle protein is accomplished in the same way as the body-cells are sensitized to or against any other foreign protein, such as egg-white, blood-serum, edestin, or zein. Before a body-cell can be sensitized to the tubercle protein or any other protein, that protein or its haptophore group must be brought into contact with the body-cell in soluble form. The result of bringing the haptophore group of the tubercle protein

into contact with body-cells is the development, in the body-cells, of a specific proteolytic ferment which splits up the tubercle protein, whether it be living or dead, whether it be an organized cell in the form of a tubercle bacillus or a solution of the tubercle protein in the form of tuberculin. It seems to me that the *modus operandi* of a solution of the tubercle protein on tissue-cells is nicely illustrated by the Calmette reaction as applied to the eye of a non-tubercular individual. When tuberculin, which is essentially a solution of tubercle protein, is applied to the eye of such a person for the first time there is no visible effect, just as there is no visible or otherwise recognizable effect from the first injection of egg-white, blood-serum, or any other soluble foreign protein subcutaneously, intra-abdominally, or intravenously into a guinea-pig or a child. But when a second instillation of tuberculin is made into the same eye of the non-tubercular person after the proper time interval, there is a more or less prompt or violent reaction, just as happens when the second injection of a like foreign proteid solution is made into the guinea-pig or the child. The first instillation into the eye of the healthy individual has developed in the tissue-cells with which it has come in contact a specific proteolytic ferment, which digests or splits up the tubercle proteid. The same thing is seen after the injection of tuberculin or its haptophore group into an individual who has a localized tubercular focus, such as a tubercular joint or lupus. The tissue-cells about the tubercular focus have already been sensitized by the autolytic products originating in the disintegrating bacilli, and the injection causes a local reaction which consists in the liberation of the proteolytic ferment stored in these cells, with the digestion or splitting up of the tubercle protein, whether it be dead or alive, organized or unorganized, within its range. When tuberculin is injected, this specific enzyme stored in the sensitized cells is in part, at least, consumed in breaking up the tubercle protein injected, and there is only a part of it left to split up and destroy the tubercle bacilli that constitute the infection. When the haptophore only is injected, the entire destructive force of the enzyme falls upon the infection. When tuberculin is injected, as the profession has learned by experience, the most benefit is derived when the smallest dose possible necessary to sensitize is employed.

In advanced general or pulmonary tuberculosis the Calmette reaction fails because the blood and possibly other fluids of the body already carry enough soluble tubercle protein to keep all the sensitized cells exhausted of their ferment, just as repeated injections of egg-white or other foreign proteids at short intervals into a guinea-pig are not followed by any reaction. To expect any good effect in these cases to follow treatment with either tuberculin or its haptophore is without justification. It is as senseless as would be the application of the whip or spur to the horse dying or dead of exhaustion. For reasons that must be evident from the foregoing it has

seemed to me that the Calmette reaction is of marked prognostic, as well as of diagnostic, value.

I may say that cell sensitization, as I understand it, easily and satisfactorily explains the fact that some non-tubercular individuals respond to the Calmette test. With the eye exposed to dust, as it is, both in and out of doors, and with other possible sources of local contamination with living or dead tubercle bacilli, and their disintegration products, it is not strange that local sensitization of the conjunctiva may occasionally result most frequently in the consumptive himself, less frequently in those associated with consumptives, and least frequently in others.

Recent studies in protein sensitization and the demonstration of the presence of a poisonous group in the protein molecule, with the study of the effect of this group on animals, have done much, as I interpret these studies, to clear up the problem of the genesis of tuberculosis, and for the first time I am able to explain, in a way satisfactory to myself at least, the effect of tuberculin in both the healthy and the tubercular animal. In the treatment of tuberculosis I prefer to employ the non-poisonous sensitizing or haptophore group of the tubercle protein molecule, for reasons already made plain, but I think that the *modus operandi* is in essence the same whether the unbroken molecule or its sensitizing part be used, just as one may sensitize a guinea-pig to egg-white with either the unbroken protein or its non-poisonous portion. However, while some light has been thrown upon the genesis and nature of tuberculosis, the problem is still far from complete solution. The size of the sensitizing dose in the treatment of the disease, in order to get the best results, is still undecided. Certainly when tuberculin is used the dose must be the smallest possible necessary to sensitize. It is also certain that when the tissue-cells have reached the stage of exhaustion or the body has been placed in the negative phase, the employment of any derivative of the tubercle bacillus in the treatment of the disease is without warrant, at present at least. Furthermore, it has been frequently demonstrated, both in animal experimentation and in the treatment of the disease in man, that this negative phase in which the body is absolutely without resistance to the bacillus can be induced by overtreatment with tuberculin. The same helpless condition can be established by the employment of large doses of the haptophore, especially when administered at short intervals. The time interval between doses is possibly of even greater importance than the size of the dose. Time is required for exhausted cells to recover their function. The guinea-pig that has received one injection of egg-white is in a negative phase for about ten days, and if, after that time, the animal is given a second non-fatal dose of the same protein, a longer, but as yet undetermined, period must elapse before the animal passes into the positive or active phase again. These intervals, necessary for the development of an active phase, apparently

differ with the protein employed and the animal subjected to the treatment, and with the tubercle protein they have not been determined in either the experimental animal or in man.

La Quimica del Bacilo de la Tuberculosis.—(VAUGHAN.)

El bacilo de la tuberculosis ha sido cultivado en grandes cantidades y después de desembarazarlo de la grasa, cera y otras substancias solubles en el alcohol y el éter, las partes tóxicas y no tóxicas de éste son separadas por medio de una solucion alcoholica alcalina. Los productos tóxicos matan a los animales en pocos minutos en la dosis de 75 a 100 milígramos. Los productos no tóxicos hace a los animales sensibles a la tuberculosis, mas esta carece de la acción venenosa. Los productos no tóxicos han sido usados y aun se usan en el tratamiento de la tuberculosis en el hombre, sinembargo no es tiempo todavía de decir si esta es superior ó no a la tuberculina de Koch.

La Chimie du Bacille de la Tuberculose.—(VAUGHAN.)

Le bacille de la tuberculose a été produit en grande quantité, et, après avoir été débarassé des matières grasses, de la cire et d'autres substances solubles dans l'alcool et dans l'éther, il est divisé par une solution alcoolique d'alcali en poison et en une partie ne contenant pas de poison. La portion qui contient le poison tue les animaux en quelques minutes, quand on le donne en doses de 75 à 100 mg. La portion qui ne contient pas le poison prédispose les animaux au bacille tuberculeux, mais n'a pas d'action virulente. La portion qui ne contient pas de poison a été employée et est employée dans le traitement de la tuberculose chez l'homme. Toutefois il est encore trop tôt pour établir si elle est préférable ou non à l'ancienne tuberculine pour ce traitement.

Chemisches Verhalten des Tuberkelbacillus.—(VAUGHAN.)

Der Tuberkelbacillus wurde in grosser Quantität kultivirt, und nach dessen Befreiung von Fetten, wachsartigen und anderen in Alkohol und Äther lösbaren Bestandteilen, durch eine alkoholische Lösung eines Alkalis in einen giftigen und einen nichtgiftigen Teil zersetzt. Der giftige Teil tötet Tiere im Verlaufe einiger Minuten, wenn er in der Dose von 75 bis 100 Milligram gegeben wird. Der nichtgiftige Teil macht die Tiere für den Tuberkelbacillus empfindlicher, hat aber keine giftigen Folgen. Der nichtgiftige Teil ist in der Behandlung der menschlichen Schwindsucht gebraucht worden und wird auch jetzt angewendet. Jedoch ist es zu früh zu entscheiden ob die Anwendung dieses Mittels besser als das alte Tuberkulin ist.

ON THE ACTION OF SOAPS UPON THE VITALITY AND IMMUNIZING PROPERTY OF BACILLUS TUBERCULOSIS.

By Hideyo Noguchi, M.D.,
From the Rockefeller Institute for Medical Research, New York.

The bactericidal action of the various body-fluids is one of the incontrovertible facts developed by the modern study of bacteriology. The nature of the bactericidal substances in lymph and blood-serum has been established biologically, but not chemically. We are still ignorant of the precise nature of the bactericidal substances, although we are acquainted with many of their properties. Nor is this to be wondered at, when we consider the great variety of substances contained in the blood-plasma and the great complexity and lability of many of them. The tissue-cells are also bactericidal. That property is possessed by certain motile cells (leukocytes) which form at some stage of their existence parts of certain tissues (bone-marrow) and certain fixed cells (endothelia) which are chiefly fixed in all parts of the body, although from them motile phagocytic elements may possibly be derived.

Lymph and blood-serum are actively bactericidal under conditions which are not strictly living ones, while phagocytes are bactericidal under strictly living conditions. On the other hand, many other body-cells than these capable of acting as phagocytes possess bactericidal properties which come to be exhibited especially after their death. In other words, the dissolution of cells is associated with an increased or renewed bactericidal power. This post-mortem bactericidal power is best exhibited by organs which are permitted to undergo aseptic autolysis. The products formed in this process possess bactericidal properties of high degree.

Conradi, who was the first to note the bactericidal effects of autolyzed tissues, describes the active substances as coctostabile, devoid of reducing power, filtrable through porcelain, unabsorbable by animal charcoal, starch and lycopodium, diffusible through parchment, and soluble in alcohol, from which solutions it is precipitable by ether. In addition, it was said to give the various positive tests for aromatic proteid derivatives. The actual active body could not be secured.

Bartel and his co-workers ascertained that the autolytic products derived from lymphatic tissues were active upon tubercle bacilli, which they attenuated in virulence when permitted to act for many days. Both the human

and bovine types of bacilli were thus acted upon by autolyzed lymphatic tissue; and animals injected with such avirulent or feebly virulent cultures were often protected from subsequent inoculation of virulent bacilli.

My own studies were led up to, not from a consideration of Conradi's and Bartel's work particularly, but from a previous study of the complement-like property of soaps in hemolysis and bacteriolysis, concerning which I have already written. I had found that soaps were extremely injurious to certain bacteria, among which were B. typhosus and B. anthracis, and that the bactericidal property was completely restrained by inactivated blood-serum. In choosing the tubercle bacillus upon which to test further the soaps, I was influenced by the notion that the fatty or waxy envelop of the tubercle bacillus might be penetrated by the soaps rather better than by other agents in aqueous solution, and the injury might be more subject to graduation and control. This conjecture proved to be well founded, as I will now relate.

When we consider the description of the bactericidal bodies given by Conradi, we may readily identify them as belonging to the soaps in a general way, and the active product employed by Bartel surely contained various soaps. The wide dissemination of fats, lipoids, and lipolytic enzymes in the tissues provides the very conditions for the free production of fatty acids during the catabolic changes in tissues; and the coincident activities, under these conditions, of the proteolytic ferments of the tissues supply the organic bases for union of the liberated fatty acids into soaps, a part of which also unite with inorganic bases in the tissues; and the gradual chemical cleavage, in air and light, of higher fats and lipoids into lower fatty acids, also plays a part.

Whether a similar action to the one produced by autolytic extracts ever takes place in living tissues, I am unable to say. We know now that there is going on generally throughout the body a breaking down and building up of fat into and from the fatty acid radicles. It is not established, however, that the soaps exist generally in the humors in such a state of activity to be an efficient cause of bacteriolysis. The facts may be quite otherwise in local foci in which tissue elements, injured by the tubercle bacillus, are degenerating. The autolytic changes going on in tuberculous tissue may conceivably liberate and produce soaps in such amounts as to be actively destructive to the contained bacilli.

In view of these circumstantial possibilities, and a few established pathological and bacteriological facts bearing upon this line of thought, I have undertaken to determine directly whether some soaps, especially the oleic acid compounds, have a bactericidal effect upon B. tuberculosis. I have also extended my observations to the possibility of developing artificial immunity in animals treated with the bacilli, after devitalization of the

organism by means of bactericidal oleic soaps. The results are given in the following protocols:

EXPERIMENTS—GROUP 1.

ANIMAL EXPERIMENTS CONCERNING THE ANTIBACTERIAL PROPERTIES OF OLEATE SOAPS UPON BOVINE AND HUMAN TYPES OF B. TUBERCULOSIS.—The antibacterial properties of oleate soaps (sodium, neurin, and ammonium oleates) were tested by inoculating a large amount, usually 0.5 to 1 c.c., of thick emulsion of B. tuberculosis, in soap solution, into guinea-pigs. These emulsions were very thick, and were kept for about twenty-four hours at 37° C. before being used for inoculations. In this series of experiments no cultural tests for the vitality of the tubercle bacilli treated with different strengths of various soaps were made, and nothing definite can be said as to whether these antibacterial properties are due to bactericidal action or to attenuating effect of the soaps.

Four strains of bovine type and one of human type were studied. The results obtained show that the virulent strains of B. tuberculosis of either type become so modified by these soaps that they often fail to produce tuberculosis in guinea-pigs. In many cases tuberculosis becomes manifest in a much milder way and progresses very slowly. Death, when it occurs, is invariably much later than in the control animals. In the guinea-pigs which escaped the tuberculous infection from the "soaped" bacilli there is unquestionably an immunity developed.

BOVINE TYPE.

$\frac{N}{200}$. *Sodium Oleate and Bovine X.* (*Contact twenty-four hours.*) 2 : 11 : '07. One guinea-pig inoculated with the "sodium oleate" culture, then treated for several successive alternate days, showed no tuberculous lesions during the observation period of one hundred and fifty-nine days.

$\frac{!N}{200}$. *Neurin Oleate and Bovine X.* (*Contact twenty-four hours.*) One guinea-pig similarly experimented on. After seventy-five days the animal, which was apparently well, was chloroformed and examined. No tuberculous lesions found.

$\frac{N}{200}$. *Ammonium Oleate and Bovine X.* (*Contact twenty-four hours.*) One guinea-pig similarly experimented on. After seventy days it died, showing typical lesions of tuberculosis.

Controls all died of typical tuberculosis in forty-six and sixty-six days respectively. The culture treated with $\frac{N}{200}$ soap solutions caused no infection or only mild lesions in guinea-pigs.

One per cent. Sodium Oleate and B. I. Ravenel. Type doubtful. (*Contact twenty-four hours.*) 3 : 12 : '07. One guinea-pig injected. Showed no symptoms of tuberculosis. Found to be refractory to a fresh inoculation with virulent culture (not treated with the soap).

One per cent. Neurin Oleate and B. I. Ravenel. (*Contact twenty-four*

hours.) One guinea-pig injected. Died in one hundred and forty-eight days of general tuberculosis.

One per cent. Ammonium Oleate and B. I. Ravenel. (*Contact twenty-four hours.*) One guinea-pig injected. No tuberculous lesions developed. Later experiment showed immunity against fresh injection.

Controls (three) died of tuberculosis in thirty-eight, thirty-five, and thirty-eight days. Immunity seems to have developed in the vaccinated pigs. The "neurin oleate" pig showed a much milder infection than the controls.

One per cent. Sodium Oleate and Bovine B. (*Contact twenty-four hours.*) 3 : 12 : '07. One guinea-pig inoculated with Bovine B. strain, treated with sodium oleate, showed a peanut-sized swelling of lymphatic gland near the site of inoculation after forty-seven days. The pig was chloroformed and examined for the extent of tuberculous lesions. Several small spots on the spleen, but the liver was quite free. From the spleen inoculations were made on two guinea-pigs (4 : 25 : '07), which died of tuberculosis in eleven days and one hundred and four days respectively.

One per cent. Neurin Oleate and Bovine B. (*Contact twenty-four hours.*) One guinea-pig inoculated with Bovine B., treated with neurin oleate, died in fifteen days of non-tuberculous disease.

One per cent. Ammonium Oleate and Bovine B. (*Contact twenty-four hours.*) One guinea-pig injected. It lived several months with some swollen glands, but without abscesses.

Controls died of tuberculosis in twenty and forty-four days respectively. The guinea-pigs inoculated with the "soap" culture showed much milder infection than the controls.

One per cent. Neurin Oleate and Bacillus H. Ravenel. (*Contact twenty-four hours.*) 4 : 6 : '07. Two guinea-pigs inoculated with H. Ravenel strain, treated with neurin oleate, died of tuberculosis in forty-six and ninety days respectively. Controls (three) died in forty, forty, and thirty days. The lesions of the neurin oleate pigs were decidedly much milder than in the control pigs.

One per cent. Ammonium Oleate and Bacillus H. Ravenel. (*Contact twenty-four hours.*) 4 : 6 : '07. Two guinea-pigs inoculated with B. H. Ravenel, treated with ammonium oleate, did not show any tuberculosis. One survived, and the other died of non-tuberculous disease after one hundred and seventy-three days. Three controls died of tuberculosis in thirty to forty days.

The treatment of H. Ravenel strain with ammonium oleate prevented infection in guinea-pigs (probably the bacilli were killed). In case of neurin oleate tuberculosis of milder grade developed.

Action of oleate soaps on caseous mass of tuberculous lesion of guinea-pig. 4 : 26 : '07. The material was obtained from guinea-pigs suffering from Bovine B. X. The caseous mass was suspended in saline solution, whence definite quantities were mixed with 1 per cent. solutions of different

soaps. At the end of eighteen hours, inoculations were made in guinea-pigs. Control guinea-pig died in fifty-two days; "sodium oleate" pig died in seventy-two days; "neurin oleate" pig died in ninety-six days; "ammonium oleate" pig escaped infection.

The material treated with 1 per cent. ammonium oleate for eighteen hours failed to produce tuberculosis in guinea-pig. The materials treated with other soaps caused death much later than the untreated material.

Human Type.

Neurin Oleate and H. 38. (*Contact twenty-four hours.*) 3 : 12 : '07. One guinea-pig inoculated with H. 38 strain, treated with neurin oleate, died of general tuberculosis in forty-two days.

Sodium Oleate and H. 38. One guinea-pig treated with sodium oleate died of typical lesions in seventy-seven days.

Ammonium Oleate and H. 38. (*Contact twenty-four hours.*) One guinea-pig similarly treated (with ammonium oleate) died of typical lesions in eighty days.

Three control guinea-pigs died of tuberculosis in fifty-four, thirty-four, and forty-two days respectively. H. 38 strain seems to be more resistant to the bactericidal properties of oleate soaps.

Development of Immunity.

H. Ravenel Strain. (*Bovine Type.*) Two guinea-pigs inoculated with the H. Ravenel strain, killed with sodium oleate, did not show any tuberculous symptoms within about three months (4 : 6 : '07 to 7 : 3 : '07). These were inoculated with large amount of H. Ravenel culture on 7 : 3 : '07. Two controls were inoculated also. The controls died of typical tuberculosis in thirty-six and twenty-five days respectively. On the other hand, the vaccinated guinea-pigs remained well for at least fifty days, then emaciation started. Both missing on my return from vacation.

B. I. Ravenel Strain. (*Bovine Type.*) Two guinea-pigs, inoculated with the soaped culture, on 3 : 12 : '07, were still healthy on 7 : 3 : '07. These were inoculated with fresh culture of B. I. Ravenel strain on 7 : 3 : '07. Two control pigs were inoculated at the same time. After a period of over three months one died of non-tuberculous disease. Autopsy did not reveal any foci of tuberculosis. The second pig still remains unaffected by tuberculosis. The two controls died of typical tuberculosis in twenty-two days and in thirty-six days respectively.

These instances are the few in which immunity seems to have developed beyond any question.

EXPERIMENTS—GROUP 2.

Cultural and Animal Experiments Concerning the Antibacterial Properties of Various Oleate Soaps and Their Components upon B. Tuberculosis.—Three strains of bovine type, one strain of human type, one strain of frog tuberculosis, one strain of avian type, and one strain of fish tuberculosis were studied.

The actions of soaps were tested either (1) by mixing them with suitable nutrient media and inoculating the virulent, vigorously growing strains on these media, and (2) by pouring solutions of these soaps into the growing cultures of the tubercle bacilli on veal bouillon glycerin-agar slants until the colonies were completely immersed under a deep layer of soap solution. Then, at the end of varying lengths of time, the colonies were fished out, and, after being suspended in saline solution for some hours to liberate the soaps, the bacilli were inoculated upon suitable media (no soaps, of course) and also into guinea-pigs.

The results obtained show that these soaps are actively bactericidal and can devitalize the tubercle bacilli completely if applied in adequate concentrations. Sodium oleate appears to be the most active agent. The constituent components of oleate soaps are unable to kill the bacilli when used in concentrations (calculated to normality) corresponding to the lower effective concentrations of the soaps. Pure oleic acid seems to have a marked bactericidal power if allowed to act for a long time. Sodium hydroxid in $\frac{N}{40}$ has only slight injurious action upon the bacilli, whereas sodium oleate destroys them in that concentration. In some instances animal experiments were positive, whereas cultural tests failed to get a growth with "soaped bacilli."

Bactericidal Power of Oleate Soap and its Components.

Soaking (immersing) the growing culture in sodium oleate, sodium hydroxid, and oleic acid. Slant cultures of Bovine B. strain, grown on veal bouillon glycerin-agar for one month (7 : 6 : '07 to 8 : 6 : '07), were filled up with 2 per cent. sodium oleate, or 0.4 per cent. sodium hydroxid, or 2.84 per cent. oleic acid emulsion. At the end of one day, six days, and fourteen days, transplantations were made to regular veal bouillon glycerin-agar slants. The results obtained were as follows:

CULTURAL TESTS.

Sodium oleate immersion (2 per cent.):

1 day's contact	No growth after 40 days.
6 days' "	No growth after 34 days.
14 days' "	No growth after 20 days.

Sodium hydroxid immersion (0.4 per cent.):

1 day's contact	Grown well after 40 days.
6 days' "	Grown poorly after 34 days.
14 days' "	Grown poorly after 20 days.

Oleic acid emulsion immersion (2.84 per cent.):

1 day's contact	Grown poorly after 40 days.
6 days' "	Growth doubtful after 34 days.
14 days' "	No growth after 20 days.

BACTERICIDAL POWER OF OLEATE SOAP.

(*Veal bouillon glycerin-agar slants made July* 24, 1907.)

	Bovine Type.			Human Type.
	H. Ravenel.	B. I. Ravenel.	Bov. B.	H. 38.
Two per cent. sodium oleate 1 c.c., to agar 6 c.c.	8 : 5. No growth.	8 : 5. No growth.	8 : 5. No growth.	8 : 5. No growth.
	8 : 8. No growth.	8 : 8. No growth.	8 : 8. No growth.	8 : 8. No growth.
	9 : 27. No growth.	9 : 29. One tube sterile. One tube few small colonies.	9 : 29. Few small restricted colonies.	9 : 29. A few single colonies.
0.3 c.c.	8 : 5. Slight growth.	8 : 5. Slight growth.	8 : 5. Slight growth.	8 : 5. Slight growth.
	9 : 29. Much restricted growth. Colonies very thick.	9 : 29. Growth fair, but less than control.	9 : 29. Restricted colonies.	9 : 29. Restricted growth.
0.1 c.c.	8 : 5. Good growth.	8 : 5. Good growth.	8 : 5. Good growth.	8 : 5. Good growth.
Control	8 : 5. Good growth.	8 : 5. Good growth.	8 : 5. Good growth.	8 : 5. Good growth.

Bacillus H. Ravenel did not grow on the first series at all, while the rest grew after three or four weeks in restricted forms. The addition of 0.3 c.c. of 2 per cent. oleate soap solution had a certain inhibitory action, which, after one month, was overcome by the bacilli to a great extent.

BACTERICIDAL POWER OF OLEATE SOAPS AND OF CALCIUM CHLORID.

(*Veal bouillon glycerin-agar slants made July* 1, 1907.)

	Bovine Type.		Human Type.
	H. Ravenel.	B. I. Ravenel.	H. 38.
Five per cent. sodium oleate 1 c.c., to agar 6 c.c.	7 : 29—28 days. No growth.	No growth.	No growth.
Five per cent. calcium oleate 1 c.c., to agar 6 c.c.	7 : 29—28 days. No growth.	No growth.	No growth.
Five per cent. calcium chloride 1 c.c., to agar 6 c.c.	7 : 29—28 days. Good growth.	Good growth.	Good growth.
Control	7 : 29—28 days. Good growth.	Good growth.	Good growth.

(*Veal bouillon glycerin-agar slants made July 9, 1907.*)

	Bovine Types.			Human Type.
	H. Ravenel.	B. I. Ravenel.	Bovine B.	H. 38.
Two per cent. sodium oleate 2 c.c.	7 : 29—20 days. No growth.	No growth.	No growth.	No growth.
1 c.c.	No growth.	No growth.	No growth.	No growth.
1.2 per cent. calcium oleate 1 c.c.	7 : 29—20 days. No growth.	No growth.	No growth.	No growth.
1.2 per cent. calcium chloride 1 c.c.	7 : 29—20 days. Good growth.	Good growth.	Good growth.	Good growth.
Control	7 : 29—20 days. Good growth.	Good growth.	Good growth.	Good growth.

EXPERIMENTS—GROUP 3.

Bactericidal Power of Oleate Soap.—*Effects of Sodium Oleate Solution upon the Growing Cultures.*—Bacillus H. Ravenel (very virulent strain of bovine type) was grown on veal bouillon glycerin-agar slants for three weeks, then the cultures were covered with soap solution of varying concentrations. Transplantations were made from time to time into new soap-free media for the purpose of determining the viability of the soaped B. tuberculosis.

Transplanted July 29, 1907, after one to seven days' immersion.

	Twenty-four Hours.	Seven Days.
Two per cent. sodium oleate solution	9 : 29—2 months. No growth.	9 : 29—2 months. No growth.
0.5 per cent	No growth.	No growth.
0.2 per cent	No growth.	No growth.
0.04 per cent	8 : 15—17 days. Poor growth.	8 : 15—17 days. Poor growth.
	9 : 29—2 months. Good growth.	9 : 29—2 months. Good growth.
Control in saline solution	8 : 15—17 days. Good growth.	8 : 15—17 days. Good growth.

The virulence of the soaped cultures was tested on guinea-pigs at the end of seven days.

Animal Experiments with the Soaped Cultures.—B. tuberculosis H. Ravenel was treated with solutions of sodium oleate for seven days and then inoculated subcutaneously near the inguinal region.

Culture treated with 2 per cent. sodium oleate:

Three guinea-pigs all survived, showed no swelling of glands, etc. Killed for examination after two months. Showed no tuberculous lesions.

Sodium oleate treatment (0.5 per cent.):

Three guinea-pigs all survived until 10 : 24 : '07, when they were found to be free from tuberculous lesions.

Sodium oleate treatment (0.2 per cent.):*

Three pigs all died of tuberculosis in forty, forty-three, and forty-six days respectively. Autopsies revealed typical lesions.

Sodium oleate treatment (0.04 per cent.):

Three pigs all died of tuberculosis in twenty-five, twenty-eight, and forty-seven days respectively.

Saline solution treatment (controls):

Three pigs all died of tuberculosis in forty-eight, thirty-two, and twenty-eight days respectively.

EXPERIMENTS—GROUP 4.

Effects of oleate soaps upon viability and virulence of B. tuberculosis (Bovine B.).

(A) Cultural Tests.

Veal bouillon with 0.3 per cent. of oleate soaps becomes so modified that flaky colonies of B. tuberculosis from other bouillon culture (without soaps) cannot be floated. In order to prevent sinking of the transplanted colonies in the soap-containing bouillon, I employed disks of cork, upon which the colonies were placed. After seventy-one days (4 : 29 to 7 : 9 : '07) the cultures were examined and found to show no sign of development. In the control there was some growth. From each culture a new culture was made on veal bouillon glycerin-agar slant, with a view to ascertaining their vitality. The following results were obtained:

Sodium oleate bouillon culture (0.3 per cent.):

No growth in thirty days after transplantation.

Ammonium oleate bouillon cultures (0.3 per cent.):

No growth in thirty days after transplantation.

Neurin oleate bouillon culture (0.3 per cent.):

No growth in thirty days after transplantation.

Oleic acid bouillon culture (0.3 per cent.):

Moderate growth in fourteen days. Good growth in thirty days.

Plain (control) bouillon culture:

Moderate growth in fourteen days. Good growth in thirty days.

Animal experiments were made with these soaped cultures, and they were found to be still alive.

(B) Animal Experiments.

Cultures from sodium oleate bouillon, ammonium oleate bouillon, and neurin oleate bouillon (each, 0.3 per cent.) were able to produce glandular

* No culture was obtained from this tube.

swellings and death in guinea-pigs. Death occurred within seventy-four, seventy-eight, eighty-two, and one hundred and three days. Guinea-pigs receiving the bacilli from soap-free bouillon culture died within fifty-one and forty-nine days. There were considerable differences between the severity of tuberculous lesions in the two series of animals.

Bovine B. strain is less virulent than H. Ravenel.

EXPERIMENTS—GROUP 5.

Soaking the growing culture of B. tuberculosis (H. Ravenel, bovine type) in sodium oleate, sodium hydroxid, and oleic acid.

Soaking started on August 15th and continued until August 20, 1907. At the end of five days transplantations were made into veal bouillon glycerin-agar slants. The results were as follows:

2 per cent. *sodium oleate* (ca. $\frac{N}{15}$)..No growth (9:27) = 37 days.
0.2 per cent. *sodium oleate* (ca. $\frac{N}{150}$).No growth (9:27) = 37 days.

4 per cent. *sodium hydroxid* ($\frac{N}{1}$)...No growth (9:27) = 37 days.
0.4 per cent. *sodium hydroxid* ($\frac{N}{10}$)..Poor growth (9:27) = 37 days.
0.04 per cent. *sodium hydroxid* ($\frac{N}{100}$).Poor growth (9:27) = 37 days.

Pure oleic acid .....Growth doubtful (9:27) = 37 days.

0.9 per cent. *saline solution* .....Good growth (9:27) = 37 days.

This series of experiments shows that oleic acid and sodium hydroxid have much less active bactericidal powers than sodium oleate, which was found to be very active here.

Animal Experiments.

Tests for vitality of the foregoing cultures after the soaking in soap and other solutions (H. Ravenel strain):

(1) 2 *per cent. sodium oleate treatment* (soaking) for five days.

August 20th. Five guinea-pigs were inoculated with the cultures (very large quantity) subcutaneously. All but one survived. No symptoms developed up to four months. One pig died in eight days of non-tuberculous cause.

(2) 0.2 *per cent. sodium oleate treatment* (soaking) for five days.

August 20th. Five guinea-pigs were inoculated. Some swollen glands in the inguinal region were observed in all pigs after thirty-six days. Pigs gained weight in the mean time. After two months some abscesses formed, without showing general infection. During the winter many died of non-tuberculous diseases (epidemic). Autopsies showed some small disseminated tuberculous nodules on spleen and liver.

(3) *Pure oleic acid treatment* (soaking) for five days.

August 20th. Three guinea-pigs were inoculated. One died of unknown cause (not tuberculosis); two survived as long as sixty days.

(4) *Sodium hydroxid treatment* (soaking) for five days.

4 per cent. solution. Four guinea-pigs were inoculated. All died of tuberculosis after two to three months. Abscesses of the glands were constant in these cases.

0.4 per cent. solution. Three guinea-pigs were inoculated. All died of tuberculosis. Average in fifty days.

0.04 per cent. solution. Three guinea-pigs inoculated died in thirty-six, forty-five, and twenty-nine days respectively.

(5) *Saline solution* (soaking) for five days.

Four guinea-pigs inoculated. All died in thirty-one, thirty-six, twenty-five, and twenty days respectively.

EXPERIMENTS—GROUP 6.

To 6 c.c. of veal bouillon glycerin-agar varying quantities of sodium oleate, oleic acid, and sodium hydroxid were added and solidified in slant position. Inoculation was made with H. Ravenel strain (bouillon culture growing for one month).

8:6:'07. Amount per tube, 6 c.c each	Two per cent. sodium oleate ($\frac{N}{15}$).	Sodium hydroxid 0.4 per cent. ($\frac{N}{10}$).	Oleic acid 2.84 per cent. ($\frac{N}{10}$).
2 c.c.	8 : 15—9 days. No growth. 9 : 27—52 days. No growth.	8 : 15—9 days. Good growth. 9 : 27—52 days. Luxuriant growth.	8 : 15—9 days. Growth doubtful. 9 : 27—52 days. Good growth somewhat restricted.
1 c.c.	8 : 15—9 days. No growth. 9 : 27—52 days. One tube sterile.	8 : 15—9 days. Good growth. 9 : 27—52 days. Like controls.	8 : 15—9 days. Good growth. 9 : 27—52 days. Good growth, but less than control.
0.4 c.c.	8 :15—9 days. Growth doubtful. 9 : 27—52 days. Several highly restricted colonies grown.	8 : 15—9 days. Good growth. 9 : 27—5 days. Like controls.	8 : 15—9 days. Good growth. 9 : 27—52 days. Covered with continuous colonies.
Control	8 : 15—9 days. Good growth. 9 : 27—52 days. Covered with continuous colonies.	.. ..	.. ..

Sodium oleate in ratio of 2 per cent. solution to culture-media 6 c.c. (equal about $\frac{N}{60}$) stops growth of B. tuberculosis, but sodium hydroxid or oleic acid in $\frac{N}{40}$ cannot stop it.

ANTIBACTERIAL PROPERTIES OF OLEATE SOAP AND ITS COMPONENTS.

Strains tested were avian, fish, and frog tubercle bacilli, the technic being similar to that in the foregoing series with bovine tubercle bacilli.

Inoculation made August 6, 1907.
Observation ended October 23, 1907.

	2 Per Cent. Sodium Oleate.				0.4 Per Cent. Sodium Hydroxid.				2.84 Per Cent. Oleic Acid.			
	2 c.c.	1 c.c.	0.3 c.c.	0	2 c.c.	1 c.c.	0.3 c.c.	0	2 c.c.	1 c.c.	0.3 c.c.	0
Avian tubercle bacilli	—	—+	+	+ + +	+ + +	+ + +	+ + +	+ + +	+	+ +	+ + +	+ + +
Pisces tubercle bacilli	—	+	+ +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +
Frog tubercle bacilli	—	+	+ +	+ + +	+ + +	+ + +	+ + +	+ + +	+ +	+ + +	+ + +	+ + +
Bovine B.	—	—	+	+ + +	+ + +	+ + +	+ + +	+ + +	+	+ +	+ + +	+ + +

Sodium oleate exerts less inhibitory influence upon the growth of B. tuberculosis of cold-blooded animals than upon those of warm-blooded animals. NaOH and oleic acid alone are almost inactive when used in corresponding concentrations.

Résumé.

As will be seen from the results presented in the foregoing experiments, the various salts of oleic acid possess a marked bactericidal property on various types of B. tuberculosis. It must be noted that the bactericidal property of these salts (or soaps) are not inherent in their component constituents to the same degree as in the compounds. From this it seems probable that the superior antibacterial activity of these soaps is to be ascribed to the changes in physical properties which accompany the formation of oleic soaps, namely, acquisition of higher permeability toward the wax-like coat of the bacillus.

The vaccination of guinea-pigs with the tubercle bacilli devitalized with oleic soaps develops in these animals a complete or partial resistance to a subsequent inoculation with a virulent culture of the same strain of B. tuberculosis. In short, a state of immunity against B. tuberculosis can be produced in guinea-pigs by means of injections of bacillary emulsion killed by oleic soaps.

BIBLIOGRAPHY.

1. Conradi: Ueber die Bildung bakterizider Stoffe bei der Autolyse, Hoffmeister's Beiträge z. chem. Physiologie und Pathologie, 1902, i, 193.
2. Bartel und Neuman: Leucocyt und Tuberkelbacillen, Centralbl. f. Bakt., etc. I. Abt., Originale, 1906, xl, 518, 723.
3. Bartel: Zur Biologie des Perlsuchtbazillus, Wien. klin. Woehensehr., 1907, xx, 155.
4. Bartel: Ueber den Einfluss der Hefen- und Kleiesäure auf die Virulenz menschlicher Tuberkelbazillen, Wien. klin. Woehenschr., 1907, xx, 1040.
5. Noguchi: Ueber gewisse chemische Komplementsubstanzen, Bioch. Zeitschr., 1907, vi, 327.

Wirkung von Seifen auf den Tuberkelbazillus.—(NOGUCHI.)

Verschiedene bestimmte Reihen von Versuchen wurden gemacht:

Erstens: Ölsaure Seifen in geeigneter Konzentration haben die Eigenschaft, virulente Tuberkelbazillen so zu verändern, dass wenn dieselben nachträglich Meerschweinchen eingeimpft worden sind, dieselben entweder vollständig verfehlen, tuberkulöse pathologische Veränderungen zu machen, oder die Veränderungen sind viel leichter als in den Kontrolltieren. Wenn der Tod in den mit den behandelten Bazillen geimpften Tieren doch durch die Tuberkulose eintritt, geschieht es unveränderlich viel später, als in den Kontrolltieren.

Zweitens: Meerschweinchen, die nach Überimpfung mit Oleaten behandelten Bazillen keine tuberkulöse Veränderung entwickeln, erwerben als ein Resultat der Impfung einen gewissen Grad von Immunisation gegenüber kräftigen und sonst virulenten Kulturen von Tuberkelbazillen. Die widerstandsfähigen Meerschweinchen entwickeln entweder keine Veränderungen nach der Einimpfung mit grossen Mengen virulenter Kulturen, oder Veränderungen von bei weitem milderen Grade und von langsamerer Entwickelung als in den Kontrolltieren.

Drittens: Ölsaure Seifen besitzen deutlich bakterizide Eigenschaften für den Tuberkelbazillus. Der Zusatz von Seifen zu sonst günstigen Kulturmedien verhindert das Wachstum des Tuberkelbazillus, selbst wenn auch die Menge klein war. Seifenlösung mit emulsierten Bazillen in Verbindung gebracht, vermindert ihre Fähigkeit in Kulturen zu wachsen, und wirksame Infektionen in Meerschweinchen, wie schon beschrieben, zu veranlassen. Seifenlösungen in geringerer Menge als zur vollständigen Verhinderung des Wachstums notwendig, vermindern die Zahlen der sich entwickelnden Bazillen. Es besteht eine relative Beziehung zwischen der bakteriziden Eigenschaft der Seifen und der Immunität der Meerschweinchen, welche durch die Impfung mit seifenbehandelten Kulturen erzeugt worden ist.

Die bakterizide Wirkung der ölsauren Seifen ist viel grösser als die ihrer Bestandteile, Säure und Basen, und kann nicht durch die getrennten chemischen Bestandteile der Seife erzeugt werden.

Die Tuberkelbazillen der Kaltblüter sind mehr widerstandsfähig gegen die bakterientötende Wirkung der Seife als die der Warmblüter.

Viertens. Es ist schon festgestellt worden, dass die Substanzen, die man von den Organen nach Autolyse vorfand, lebhaft-bakterizide sein können (Conradi), und es ist auch gezeigt worden, dass die autolytischen Produkte des Lymphdrüsengewebes dem Tuberkelbazillus schädlich sind, und ihre Virulenz abschwächen (Bartel). Die Seifen, die sich während der Autolyse bilden, dürfen einer der wichtigen Faktoren, in der Zerstörung der Bazillen und in der Abschwächung ihrer Virulenz sein.

TUBERCULO-TOXOIDIN AND IMMUNIZATION SERUM.

By Dr. T. Ishigami,

Director of the Ishigami Institute for Infectious Diseases, Osaka, Japan.

It is a great misfortune of man that there is not yet any perfect method of protection from his stubborn enemy, tuberculosis. In my belief, the only rational and promising cure for this disease in the present therapy is the bacteriological one.

As the efficacy of Koch's preparations on incipient tuberculous patients proves itself in many instances only when they are administered with a careful avoidance of the reaction, the first and natural step to be taken in our study of the cure will be for the methods to obviate the reaction.

After continuous investigations for more than ten years I have succeeded in getting two remedies of comparatively great efficacy, and free from any detrimental reaction:

(1) The one is a chemical preparation from tubercle bacilli and is applicable to incipient and feverless patients.

(2) The other is an immunization serum, and is applicable chiefly to patients in an advanced stage of the disease.

I introduced these two remedies in the belief, based on my own experience of several years, that they were harmless and effective, although not absolutely infallible, remedies for tuberculosis.

I have since received the corroboration of many practitioners equally recognizing the efficacy and harmlessness of these remedies. In this paper I will attempt briefly to describe them.

Tuberculo-toxoidin.

This preparation is made by chemically dissolving the tubercle bacilli and transforming the toxic property, thus getting rid of the reaction, which is the common detriment of all the other preparations from tubercle bacilli.

According to the modern theory of immunization, strong immunization cannot be attained without employing strong toxin. The question will, therefore, naturally suggest itself whether immunity can be imparted by employing a chemically transformed and harmless toxin.

My honored master, Professor Kitasato, and Professor Behring had succeeded in achieving their epoch-making discovery of the serum therapy of tetanus and diphtheria by first attenuating the virus by means of chemical

reagents and then by immunizing animals with it. Ehrlich's tetanus-toxoid, which is obtained by chemically treating the virulent toxin, and is harmless to animals, still retains the power to immunize them and to neutralize the antitoxin.

Considering these facts, it will be quite a natural step to apply the same principle to the subject of tuberculosis, and to expect a successful solution of it. This has been the motive of my preparing these remedies.

Moreover, from my own experience of many years I found that, for the purpose of curing tuberculosis, the bacterial immunization is necessary, and that, as the absorption of the tubercle bacilli from the subcutaneous tissue of man and animals is extremely difficult, they must first be chemically dissolved and thus made absorbable.

Method of Preparing Tuberculo-toxoidin.—The culture of the tubercle bacilli is well soaked and washed with water, so as to remove the soluble toxin. It is now thoroughly dried and weighed, and, after again washing with water, is treated with strong sulphuric acid, in order to disintegrate the bacterial body and thus to extract the inner toxin and to change its toxicity. Now, by adding a large amount of water and, after stirring, letting stand for some time, the fats and aromatic oil rise to the top, leaving the active substance in the bottom in the form of a precipitate. This precipitate is gathered on a filter-paper and well washed with distilled water until it becomes neutral. Then 0.5 gram of the dried product is dissolved in 100 c.c. of a weak alkali solution to a brown-colored, transparent liquid.

Although the preparation of tuberculo-toxoidin is such a simple matter, the duration of soaking in the sulphuric acid must carefully be regulated according to the virulence of the bacilli, otherwise the toxicity may remain still too strong, or the whole contents may be turned useless by carbonization. There is thus required more or less skill of manipulation.

This substance, when injected subcutaneously in man or animals, is easily absorbed without irritating the locality, and, as the toxic property is already changed, comparatively large doses can be injected without harm. Yet while it is harmless, it is as effective in immunizing man and animals as Ehrlich's so-called tetanus toxoid. Hence the name, "Tuberculo-toxoidin."

I will mention here the following animal experiments, in order to show the efficacy and harmlessness of the preparation:

(1) *Test of Toxicity.*—By the injection of 10 c.c. of the tuberculo-toxoidin into the peritoneal cavity of a tuberculous guinea-pig, which would have succumbed in twenty-four hours to an injection of 0.1 c.c. of Koch's old tuberculin, there was noticed no reaction. This shows clearly that it is harmless.

(2) *Prophylactic Test.*—Guinea-pigs injected subcutaneously with 1 c.c. of the toxoidin are generally found to be immune against the inoculation of the tubercle bacilli from the fourth till the fourteenth day after the operation.

(3) *Therapeutic Experiments.*—In a guinea-pig subcutaneously inoculated with tubercle bacilli, if the treatment commences within one week of the inoculation and 0.5 to 1.0 c.c. of the toxoidin be subcutaneously injected about ten times, the disease will be either cured or prevented from making further progress. If, two or three weeks after the inoculation of bacilli, the injection of the above doses be made in an animal with greatly swollen glands, the swelling subsides, the body weight increases, and the fatal period is much postponed. While a control animal dies in three months, the test animal receiving injection treatment lives over a year. When such an animal is killed, it is found by autopsy that the tubercular formations of the organs are not entirely healed; this is due to the fact that guinea-pigs are too susceptible to tubercle bacilli to admit of a complete cure.

A noteworthy fact is that in the guinea-pigs treated with the toxoidin the visceral tubercles generally show a tendency to heal, and the number of cells containing bacilli is much greater than in those which have not been thus treated. Moreover, the bacilli in the cells are small and short, evidently showing a degenerative form.

Clinical Application.—From my own experience and the reports of other practitioners who tried the preparation the following conclusions may be drawn:

(1) By injecting the preparation in a gradually increasing dose to feverless tuberculous patients, almost every one of them increases in body weight and vital capacity, and becomes conscious of the alleviation of the symptom.

(2) The bacilli in the sputum are gradually broken up and agglutinated and finally disappear, although in some rare cases a small amount of expectoration containing bacilli is found for a long time.

(3) The quantity of opsonin in the patient's blood is found to gradually increase by the injection treatment.

(4) The incipient and feverless tuberculous patients can be, almost without exception, completely cured within from three to six months by injection of this preparation.

(5) In patients in more or less advanced stage, if the nutrition is in good order, similar results can be obtained. In feverish patients a satisfactory result is often obtained by means of the injection used side by side with antipyretics. In more serious cases, beyond a certain degree, it is quite useless.

(6) Those patients who were once cured or alleviated by this treatment suffer only very seldom from the reattack.

(7) Out of the total of 772 tuberculous patients, each of whom has received more than fifteen injections of tuberculo-toxoidin in my clinic within the past few years, there were 274 who were completely cured and 258 who were partially cured. These last two figures added together make 532, being 68.91 per cent. of the total number of patients. Those who discontinued the treatment for various reasons numbered 107; those who died numbered 29; and the remnant numbered 104.

(8) Out of the total of 778 patients treated with the tuberculo-toxoidin (injected more than fifteen times) by other practitioners, there were 232 who were completely cured and 228 who were partially cured. These last two figures combined make 460, equal to 59.13 per cent. of the total number of patients. Those who discontinued the treatment for various reasons were 162; the deaths, 63; the remnant, 93.

The average number of injections per patient among those completely cured was 65.

Immunization Serum.

On the problem of serum therapy of tuberculosis the results of previous investigators, which are undoubtedly very rich, have not yet reached the stage to permit the general application on the patients. My own investigation of previous years has also failed in consequence of a difficulty of immunizing animals from tuberculosis, and of the characteristic detrimental reaction of the animal serum upon tuberculous patients. However, by means of injection of the tuberculo-toxoidin I have finally succeeded in getting an immunization serum of a comparatively strong efficacy. I have also succeeded in removing the characteristic reaction of animal serum upon tuberculous patients in the manner to be mentioned below.

When an animal serum is injected subcutaneously to tuberculous patients, there are often noticed characteristic violent reactions, such as acute urticaria of the injected locality, redness of face, palpitation of heart, increased respiration, itching of entire skin surface, and, rarely, pain of joints. All these symptoms, which disappear in five to thirty minutes, are doubtless due, as maintained by Dr. S. Ogata, to the agglutination of red blood-corpuscles.

When the serum of a goat, or a cow, or a horse is treated with 2 to 3 per cent. of table-salt, kept at 50° C. for thirty minutes, and then filtered through a Chamberland filter, it can be clearly shown under the microscope to have entirely lost the power of agglutinizing the blood-corpuscles of tuberculous patients or of healthy people, and with some exception it no longer causes any reaction, either local or general, on injection into patients.

Experiments on Animals.—When 0.1 c.c. of Koch's old tuberculin, which is the fatal dose to a tuberculous guinea-pig, is mixed with 0.025 c.c. of the immunization serum, and, after ten minutes' standing, injected subcutaneously into the tuberculous guinea-pig, there is not the slightest disorder noticed.

When the phagocytic phenomena are examined according to Dr. Wright's method, my immunization serum presents decidedly more marked phagocytic activity than other serums.

When 0.5 c.c. of the immunization serum diluted to four times its volume is subcutaneously injected every other day into a tuberculous guinea-pig

with markedly swollen lymphatic glands, the swelling remarkably shrinks after about ten injections. By further continuing this treatment the course of the disease is arrested in spite of the fact that the tubercular lesions of the organs are not yet completely healed. The microscopical sections show the bacilli engulfed in the cells, and become smaller and shorter, indicating the degeneration produced by the serum.

Clinical Application.—Generally speaking, my immunization serum does not cause, by subcutaneous injection, any local or general reaction, as already stated above; still, in some exceptional cases of idiosyncrasy, a reaction may be noticed. When, however, it is administered internally, as described in another chapter, it produces nearly the same results as by subcutaneous injection, but without any reaction. Hence, except for cases demanding quick or local results, it will be found safer and more convenient to administer it internally.

The following cases require subcutaneous injection:

(1) The cases of acute tubercular cerebral meningitis in which the exudation is not yet marked. I have three records of satisfactory cures attained by injecting the serum into children who had fallen into stupor from tubercular cerebral meningitis. I have also several records of much alleviation by the serum injection of cases of cerebral meningitis appearing in the course of pulmonary tuberculosis.

(2) The cases of tubercular peritonitis having painful indurations.

(3) The cases of tubercular arthritis complaining of pain.

In the following cases, either the injection or the internal administration is employed to suit the circumstances:

(4) In cases of pulmonary tuberculosis with high fever or with disordered nutrition, when the patients are unfit for the tuberculo-toxoidin treatment, the serum injection is first to be resorted to. When the symptoms become alleviated and the fever disappears and nutrition is restored, the tuberculo-toxoidin is injected in the usual manner.

According to the results of the serum treatment performed in my sanatorium, out of the total of 189 patients, 43 were completely cured and 63 were partially cured. These last two figures combined together make 106, being 56.08 per cent. of the total number of patients. Those who discontinued the treatment for various reason numbered 37; those who died numbered 24; and the remnant numbered 22.

(1) The average number of injection, for those who were completely or partially cured was 55 per capita.

(2) The increase and decrease of opsonin were faster in this treatment than in the tuberculo-toxoidin treatment.

(3) The body weight and vital capacity generally increase by the serum treatment.

(4) The phenomena of agglutination degeneration and diminution of the bacilli are similar to those of patients under the toxoidin treatment.

Judging from the percentage results summarized in the tables above, the result of the serum treatment appears to be somewhat inferior to that obtained with tuberculo-toxoidin. As, however, the serum is employed generally in the more serious cases, while the tuberculo-toxoidin is injected generally in less advanced cases, the above tables are not strictly comparable with each other. If the advanced patients are first treated with the serum until the symptoms are alleviated, and are then injected with tuberculo-toxoidin, a much better result is obtained.

Internal Administration of Tuberculo-toxoidin and Immunization Serum.

The subcutaneous injection of the tuberculo-toxoidin is, as is stated above, the safest and most efficacious of all the modern therapeutical methods for tuberculosis. As, however, the performance of the subcutaneous injection always requires proper precautions, there are many patients who are prevented from receiving the treatment. Moreover, there are a few patients of constitutional idiosyncrasy on whom the injection of the serum causes reaction. For these cases we are forced to resort to a simpler method of applying these cures.

I have ascertained, by experiments on animals, that the internal administration of the tuberculo-toxoidin and immunization serum is harmless and efficacious. Consequently, I have tried the same method on patients for the past few years, and found it comparatively efficacious and free from any reaction.

It is difficult to get a result by administering in the liquid state the tuberculo-toxoidin and the immunization serum. If administered in the form of pills, however, they are partially absorbed without change, as is seen from the following facts:

(1) Those patients in whom the injection of tuberculo-toxoidin causes fever are also subject to a rise of temperature by the internal administration of the toxoidin pills of comparatively large doses.

(2) Those patients in whom urticaria is produced by the injection of the serum are also susceptible to the same symptoms on administration of the serum pills in comparatively large doses.

With patients in an advanced stage, receiving the toxoidin injection, I administer at the same time the pills in the following manner:

The serum pills are given first until all the symptoms are sufficiently alleviated. The toxoidin pills are then substituted, and in the meanwhile the number of injections is gradually diminished. The administration of the pills is maintained for a long time after stopping the injections, thus to prevent the diminution of the immunity attained.

TUBERCULO-OPSONIC INDEX AND BODY-WEIGHT.

Name.	Before the Injection.		Tenth.		Twentieth.		Thirtieth.		Fortieth.		Fiftieth.		Sixtieth.		Seventieth.		Eightieth.		Ninetieth.		Remarks.
	O. I.	B. W.	O. I.	B. W.	O. I.	B. W.	O. I.	B. W.	O. I.	B. W.	O. I.	B. W.	O. I.	B. W.	O. I.	B. W.	O. I.	B. W.	O. I.	B. W.	
Unadvanced Cases.																					
Mr. S. N.....	92	55.000	120	54.000	97	54.000	76	54.100	76	54.000	112	54.000	108	54.200	125	54.000	127	..	160	..	
Mr. K. Y.....	57	45.650	60	47.000	138	46.800	136	45.200	144	45.800	144	45.800	212	45.800	213	46.800	..	..	..	..	
Mrs. T. Y.....	98	36.600	174	37.200	183	36.550	155	37.200	173	37.900	149	38.600	228	36.700	230	38.400	..	..	..	..	
Mr. T. K.....	66	43.600	98	43.600	208	43.700	154	44.100	165	43.600	190	44.300	208	45.400	198	45.400	..	..	..	..	
Mr. G. T.....	73	45.500	86	46.200	185	49.050	120	51.500	125	52.100	198	53.300	180	52.450	148	52.300	..	..	..	..	
Mr. M. S.....	94	55.100	70	55.000	94	55.650	103	55.500	100	55.000	111	54.000	116	54.600	150	54.200	162	53.600	..	..	
Mrs. S. N.....	60	50.700	63	51.000	130	50.650	165	51.500	151	50.650	175	50.450	208	50.650	207	51.250	213	51.700	184	51.100	
Mr. M. M.....	96	54.300	138	55.400	135	55.900	160	56.100	109	56.100	120	55.700	132	57.100	115	57.000	..	..	..	..	
Mr. T. N.....	100	54.000	142	55.450	162	56.300	162	56.300	200	56.400	176	56.700	166	57.300	179	57.400	158	57.800	183	57.800	
Mr. T. O.....	80	44.900	130	45.500	174	46.600	197	47.300	184	48.700	184	48.700	202	48.700	208	48.900	..	..	..	..	
Advanced Cases.																					
Miss K. N....	92	39.300	100	39.950	146	40.200	176	40.900	190	42.600	170	43.200	180	44.800	187	44.800	..	..	..	..	The injections are performed generally every other day, except some of them which have been repeated at intervals of three to five days, looking for patients' opsonic index and other conditions.
Mr. H. N.....	79	46.850	82	47.850	109	44.900	122	45.400	190	47.450	156	47.400	158	49.500	157	50.400	184	48.500	..	..	
Mr. Y. O.....	82	43.000	170	42.300	156	42.200	155	41.550	111	41.300	120	41.500	271	41.450	182	40.550	155	41.500	176	41.450	
Mr. S. O.....	98	23.200	111	23.200	109	24.600	190	24.900	152	24.050	158	25.100	178	24.550	213	25.600	194	25.600	200	25.650	
Mrs. J. M.....	91	26.800	105	26.400	120	26.500	121	26.400	148	26.500	166	26.500	175	26.100	164	26.200	164	26.050	188	26.500	
Mr. Y. H.....	65	58.200	90	58.800	100	58.600	115	58.600	124	58.850	121	58.500	132	58.300	114	57.600	120	58.300	..	..	
Mrs. H. I.....	96	33.700	104	33.800	108	34.350	128	34.400	150	35.150	154	35.700	150	36.650	158	36.850	193	37.150	161	37.950	
Mr. S. O.....	78	50.750	137	50.750	182	50.750	192	48.500	200	50.400	197	51.100	198	52.650	182	53.700	..	..	..	..	
Mr. U. A.....	80	38.350	124	38.650	116	38.350	112	38.000	144	39.000	139	38.800	146	37.200	88	36.150	155	36.650	172	36.650	
Mr. T. S.....	102	53.500	143	55.760	158	55.750	158	55.700	134	53.200	120	53.200	118	53.350	158	51.900	158	51.900	..	..	
Mr. K. Y.....	77	48.800	83	48.850	82	49.550	68	49.100	90	49.700	100	50.200	170	50.300	200	49.000	202	49.300	..	..	
Mr. I. I.....	62	45.800	62	46.500	96	47.500	71	48.000	120	48.250	118	49.150	120	48.400	126	48.100	130	47.000	..	..	
Mr. F. Y.....	84	47.500	91	47.800	90	47.900	90	48.000	100	48.100	98	48.800	100	48.800	90	49.100	100	48.600	..	..	
Mr. K. F.....	77	48.950	81	49.000	129	49.950	133	50.000	134	51.000	135	51.550	175	52.500	86	52.400	92	52.500	95	52.500	
Mrs. T. H.....	76	34.350	64	34.600	103	34.200	103	34.000	85	34.250	115	34.250	154	33.800	155	33.400	157	33.700	..	..	
Mrs. K. B.....	60	55.000	78	56.000	85	56.700	130	57.600	145	57.700	172	59.700	169	57.400	168	57.000	172	58.000	138	57.500	
Mr. S. K.....	60	54.000	64	..	62	50.500	154	52.600	172	52.500	175	52.500	172	52.800	195	53.000	196	51.500	..	..	
Mr. A. S.....	90	38.800	134	..	150	..	154	34.100	157	44.500	153	44.500	192	45.500	176	45.500	186	46.000	196	46.050	
Mr. T. K.....	80	52.050	98	52.700	107	52.700	109	54.000	109	54.000	113	53.250	105	53.800	115	54.300	118	54.000	..	..	
Mr. H. U.....	82	47.000	149	47.000	155	47.800	200	48.400	195	48.800	152	49.300	158	49.500	115	50.500	202	51.000	198	51.000	
Mrs. K. W.....	79	32.700	90	33.000	84	32.400	98	32.800	120	32.850	130	33.800	149	34.050	138	34.200	148	..	140	33.250	
Mrs. F. Y.....	92	40.500	140	42.400	197	42.600	158	43.850	135	44.050	171	44.600	130	44.800	178	44.900	..	..	..	..	
Mrs. W. M.....	60	33.700	84	33.700	114	36.000	70	35.000	210	35.600	214	35.250	220	36.200	210	36.500	200	36.300	90	35.250	
Mr. K. H.....	62	36.600	90	35.400	137	35.500	98	35.000	120	36.150	90	35.550	60	33.480	..	..	..	..	..	..	
Miss Y. M.....	55	36.150	71	36.500	80	37.000	66	36.000	107	36.000	105	35.800	109	36.000	80	35.000	70	33.000	66	33.200	

THE PART OF ENZYMES IN TUBERCULOUS LESIONS.

By Eugene L. Opie,

From the Rockefeller Institute for Medical Research, New York.

Substances formed by digestion of protein were first found in inflammatory exudates more than forty years ago; so-called peptone was found in pus by Eichwald (1864), and many observers demonstrated its presence in the urine in association with a variety of inflammatory and suppurative conditions, such as empyema, purulent peritonitis, and pneumonia. What has been described as peptone, but is now designated albumose, was found in purulent sputum by Kossel, and to explain its presence he cited an observation of Friedrich Müller, who had found that a glycerin extract of purulent sputum was capable of digesting fibrin in the presence of weak alkali.

Friedrich Müller, it is well known, has subsequently studied the autolysis of lung consolidated by the exudate of acute croupous pneumonia, and has shown that self-digestion at body temperature, under conditions which prevent the multiplication of bacteria, occurs with formation of albumose, leucin, tyrosin, and other substances which are obtained by decomposition of proteid. Nuclei disappear in the autolyzed lung, and nucleins disintegrate. These observations are believed to explain, in part at least, the disintegration and absorption of leukocytes and fibrin which fill the alveoli of the pneumonic lung. Evidence that digestion of the exudate occurs at the time of resolution is furnished by the presence of albumose and true peptone in the urine during a period shortly before and until several days after crisis (Ito).

The enzyme which Friedrich Müller first found in purulent sputum digests proteid with the greatest activity in the presence of an alkaline medium, and is peculiar to the polynuclear leukocytes in whatever situation these cells occur. By studies published several years ago I have shown that the cells of an inflammatory exudate contain a second enzyme, which is distinguishable from that of the polynuclear leukocytes by its activity in acid, whereas it fails to digest in an alkaline, medium. This enzyme is present in the large mononuclear phagocytes, which are most abundant during the later stages of inflammatory reaction. I have found it convenient to designate the first enzyme leukoprotease, the second, lymphoprotease. With acute inflammation, as with gastro-intestinal digestion, two

enzymes are concerned, and one, like trypsin, acts in the presence of alkali, whereas the other, like pepsin, acts best in the presence of acid.

The reactions which follow the invasion of the tubercle bacillus, unlike the acute inflammatory processes just mentioned, exhibit little obvious tendency to resolve and disappear. With human tuberculous pneumonia there is apparently no tendency to resolution, but, on the contrary, caseation occurs, and the tissue is converted into relatively insoluble material, which, as Müller and his pupils have shown, has the characters of coagulated albumin. Nevertheless, solution and disappearance of a tuberculous exudate may occur in animals which exhibit resistance to the invasion of the tubercle bacillus. Von Behring has found that tuberculous pneumonia in the horse may undergo resolution. Especially noteworthy are the observations of J. L. Nichols, made upon rabbits immunized by the method of Trudeau. Vaccinated animals, when inoculated intravenously with virulent tubercle bacillus, exhibit a more intense reaction than normal animals inoculated for control with the same microörganism. At the end of from nine to seventeen days the lungs of the vaccinated animal are voluminous and injected, and contain large tubercles composed of epithelioid cells, with some polynuclear leukocytes; there is no caseation, and the lesion has the appearance of pneumonia. Tubercles in the control, on the contrary, are small. In the vaccinated animals Nichols found that the reaction reaches a maximum and subsides; tubercle bacilli cannot be found; cells forming tubercles disappear, and the lungs return to normal. In the unvaccinated animals tubercles continue to increase in size, tubercle bacilli are abundant, and caseation occurs. Disappearance of the tuberculous pneumonia in the vaccinated animal is unaccompanied by caseation, and resembles resolution in acute croupous pneumonia, but, whereas in the exudate of the latter polynuclear leukocytes are predominant, in the tuberculous process mononuclear cells, the so-called epithelial cells, are in far greater number. These facts demonstrate that tuberculous pneumonia in insusceptible animals may resolve.

Little attempt has been made to study the enzymes contained in the cells, which accumulate as the result of tuberculosis, and there is no evidence to determine if enzymes have a part in the resolution of tuberculous exudates. Suggestion that the epithelioid cells of the tubercle contain proteolytic enzymes is furnished by the phagocytosis of tubercle bacilli, which are probably in part destroyed and dissolved; the same cells, moreover, occasionally ingest and destroy polynuclear leukocytes and other cellular elements.

Schmoll and Socin have found that cheesy material from tuberculous tissue consists almost wholly of proteid substance, insoluble in water; the small proportion of phosphoric acid in cheesy material has given indication

that products derived from the destroyed nuclei are quickly removed. They have found that tuberculous pneumonic lung and cheesy material undergo only trivial autolysis when incubated in normal salt solution under toluol. Matthes has examined tuberculous glands which have not undergone complete caseation, and has obtained reactions which indicate the presence of products of proteid digestion, namely, deutero-albumose and peptone. Speithoff has found albumose and peptone in extracts prepared from the non-caseous parts of tuberculous lymphatic glands, but has found these substances absent in pure caseous material, that is, living tuberculous tissue contains in small amount products of proteid digestion, whereas dead tuberculous material contains none.

With the assistance of Miss B. I. Barker I have attempted to determine if the proteid-digesting enzymes which may be demonstrated in the cells of an acute inflammatory exudate are present as well in newly formed tuberculous tissue. Autolysis of such tissue does not allow an accurate estimate of its enzymotic action when the available material is small in amount, for the proteid which is acted upon by the enzyme is limited to that of the cells which contain it. For this reason small quantities of the tissue to be tested have been allowed to act upon a fixed quantity of foreign proteid, namely, blood-serum coagulated by heat. To determine what reaction favors digestion, tests have been made in the presence of acetic acid or of sodium carbonate or of a neutral medium. Digestion has been measured by determining, with the Kjeldahl method for the estimation of nitrogen, the amount of coagulate protein converted into incoagulable products of digestion.

Tuberculous tissue has been obtained from the mediastinum of animals which have received tubercle bacilli in the pleural cavity. During the first two or three weeks after inoculation this tissue is gray white and resembles sarcoma, but later caseation occurs, and the masses which fill the mediastinum may become opaque and necrotic. These newly formed masses have the histological character of diffuse tuberculous tissue, and consist in great part of large epithelioid cells. These cells in the dog are identical in structure with the large mononuclear cells which are found during the late stages of an inflammatory reaction. During the first few weeks after inoculation polynuclear leukocytes are abundant, and often occur in small collections among the epithelioid cells. The presence of polynuclear leukocytes in the newly formed tuberculous tissue is in accord with the well-known fact that tubercle bacilli, when injected into animals, causes, like other microörganisms, accumulation of polynuclear leukocytes; these cells are soon wholly or almost wholly displaced by mononuclear epithelioid cells, and after the first few weeks the tuberculous tissue in the mediastinum contains few if any polynuclear leukocytes.

It has been shown by Biondi, Hedin and Rowland, and others, that various tissues of the body undergo autolysis with greater activity in an acid than in an alkaline medium. I have shown, some years ago, that active digestion of foreign proteid, which occurs in the presence of an alkaline medium, is caused only by tissues or exudates, the pancreas excepted, which contain polynuclear leukocytes in abundance. Tests made with tuberculous mediastinal tissue have shown that active digestion, in the presence of weak alkali (sodium carbonate), occurs with tissue removed during the first weeks of the tuberculous reaction at a time when polynuclear leukocytes are abundant; but after about the third week, when polynuclear leukocytes have diminished in number, such digestion is far less active and disappears almost completely. The tuberculous tissue contains, moreover, an enzyme which digests proteid in the presence of weak acid. This enzyme is active in tissue obtained a short time after inoculation, and is still present at a later stage, in which the enzyme of the polynuclear leukocytes has disappeared. Since the cells of this tissue are almost wholly large epithelioid cells, there is little doubt that they contain the enzyme which is constantly present in tuberculous tissue.

That this enzyme of the epithelioid cells is much more active than the similar well-known enzyme which causes autolysis of liver and of other organs, is shown by a comparison of the enzymotic activity of normal liver with that of liver thickly studded with miliary tubercles, for such hepatic tissue, obtained as the result of experimental inoculation, has caused much more active proteolysis in an acid medium than normal liver tissue.

As long as the tuberculous tissue has the gross and histological appearance of living tissue, the enzyme which digests in acid is present, but with the progress of caseation it gradually diminishes in amount, and at a time when caseation is almost complete, the enzyme exhibits only trivial activity.

The behavior of the enzymes of tuberculous tissue, in the presence of the fluid which accumulates in infected serous cavities, is of interest for the reason that the enzyme of polynuclear leukocytes, I have shown, is wholly inactive in the presence of blood-serum. This power of the blood-serum to inhibit the enzyme of the polynuclear leukocytes passes, with the serum of the blood, into the serum of the inflammatory exudate, so that the polynuclear leukocytes of the exudate are suspended in a fluid which is capable of restraining the action of their enzyme, should it be set free by disintegration of the cell or by other means. In other words, the leukocyte which acts as a phagocyte contains an enzyme which may attack bacteria or other proteid bodies ingested by the cell, but is rendered inactive as soon as it escapes from the cell body. Experiments have shown that, when suppuration occurs, the antienzymotic action of the serum is, on the contrary, overcome; increasing

quantities of enzyme, set free by disintegration of polynuclear leukocytes, are no longer restrained by antienzyme, which is present, so that the purulent fluid is capable of dissolving fibrin and necrotic tissue with which it comes in contact. Upon this property doubtless depends the solution of tissue which occurs with suppuration and causes erosion and undermining. Resolution of an inflammatory exudate, with restoration of the inflamed tissue to normal, may occur so long as the inflammatory reaction has not reached the stage of suppuration, but with abscess formation restoration to normal by disappearance of exudate is not possible, for tissue has been destroyed.

These facts, concerning acute inflammation, are recalled for the purpose of comparison with changes which occur during the progress of tuberculosis. In the tuberculous lesion, polynuclear leukocytes have a relatively inconspicuous part, whereas mononuclear cells containing an enzyme which acts with maximum activity in the presence of acid are predominant. An opportunity to study the effect of a serous exudate which accumulates as the result of tuberculous infection upon the enzymes of tuberculous tissue is afforded by the pleurisy which results when tubercle bacilli are injected into the pleural cavity of the dog. Digestion caused by tuberculous tissue obtained shortly after inoculation has been found slightly inhibited by the serum of the tuberculous effusion, whereas complete inhibition has resulted when the same enzyme is brought into contact with an equal quantity of fresh blood-serum. The tuberculous tissue which has been employed has contained both leukoprotease, the enzyme of polynuclear leukocytes, and the enzyme which digests in acid and is constantly present in living tuberculous tissue. Further tests have shown that the serum of the tuberculous exudate, like the serum of the blood, actively inhibits the enzyme of the polynuclear leukocytes, whereas it has lost the property possessed by the blood-serum to restrain an enzyme acting in the presence of acid. (Tests were made with the enzyme contained in lymphatic glands, as tuberculous tissue containing no leukoprotease was not available.)

Furthermore, the tuberculous serum not only fails to inhibit the enzyme which acts in acid, but is itself capable of proteolytic action; that is, it contains enzyme unrestrained by antienzyme. If blood-serum or the serum of an acute serofibrinous exudate, obtained by a single intraperitoneal injection of turpentine, is incubated with coagulated proteid, no digestion results, but if an equal quantity of tuberculous serum is employed, active proteolysis occurs. The experiments which have been performed indicate that proteolytic activity of the exuded tuberculous serum increases with the age of the exudate.

The experiments which have been described offer suggestions to explain some of the changes occurring in the tubercle. In the first place, it is note-

worthy that the epithelioid cells of the tubercle contain an enzyme which resembles that contained in the large mononuclear phagocytes, abundant during the late stages of an acute inflammatory reaction. Many pathologists have maintained that these cells are identical.

There are, I believe, analogies between the digestion of tissue which occurs with suppuration, and the caseation of tuberculous tissue, and it seems not improbable that the occurrence of caseation is dependent, in part at least, upon the presence of unrestrained enzymes in the tissue. With suppuration the enzymes of the polynuclear leukocytes are no longer checked by the serum which surrounds the cells. With pleural tuberculosis, changes referable to the action of the tubercle bacillus occur in the exuded serum, so that it loses its power to restrain the activity of the enzyme constantly present in tuberculous tissue. It is not improbable that the same changes occur within solid tuberculous masses, particularly since access of normal serum is impaired by the poor vascularization of tuberculous tissue. The caseous necrosis which occurs is associated with solution of nuclei, and, first affecting the epithelioid cells, later destroys the neighboring structures, so that homogeneous areas of caseation result. The enzyme of the polynuclear leukocytes causes liquefaction of tissue, whereas the weaker enzyme of tuberculous tissue causes no solution. Products of proteid digestion, nevertheless, according to the observation of Matthes and Speitoff, previously cited, are present in the tuberculous tissue, but quickly disappear after caseation has occurred. Injury to tissue is due primarily to the action of the tubercle bacillus, but the occurrence of caseation is perhaps directly referable to autolysis. Somewhat similar necrosis occurs in other conditions with which large mononuclear cells rich in enzyme, similar to that of the tubercle, are massed together. The lesions of typhoid fever are in large part accumulations of such cells, and are characterized by early necrosis. Longcope has found in typhoid lymphatic gland an enzyme which digests proteid in the presence of acid, and is similar to that which I have found in inflamed lymphatic glands containing the same type of cell.

Caseation is not an essential feature of tuberculosis. Resolution and recovery occur without destruction of tissue when the reaction has accomplished the destruction of the microörganism. Autolysis of cells which form the exudate occurs in the presence of serum capable of restraining the enzyme they contain, and their disappearance is brought about without injury to adjacent tissues. With caseation, on the contrary, the cells are transformed into insoluble material which is absorbed with much difficulty, and when the caseous area communicates with the surface of the body, ulceration results. Return to normal is possible only by new formation of tissue, for resolution or absorption of exudate, even were it possible, would not restore the infected tissue to its former condition.

El papel de los Fermentos en Lesiones Tuberculosas.—(OPIE.)

El fermento de los tejidos tuberculosos ha sido estudiado en animales inoculados en la pleura con el bacilo de la tuberculosis. El fermento peculiar a los leucositos polinucleares se observa momentos después de la inoculación, mas éste disminuye rapidamente en actividad. Un segundo fermento capaz de digerir sustancias proteolíticas, en un medio ligeramente acido, es presente en abundancia hasta que la degeneración caceosa aparese cuando este desaparese rapidamente. El suero de la exudacion que se acumula en el interior del pecho, tiene el poder de disminuir ó abolir la acción del suero de la sangre, ó de otros fermentos por el estilo. El fermento que actua en un medio acido, presente en las celulas epiteliales del tuberculo (paresido al fermento de las celulas grandes mononucleadas), comunes en la exudación de las inflamaciones, puede producir otolisis en la ausencia de un abastecimiento suficiente de circulacion, y esto explica el fenómeno de la degeneracion caceosa en los tejidos que contienen los productos del bacilo de la tuberculosis y que tienen una vascularizacion pobre.

Le rôle des enzymes dans les lésions tuberculaires.—(OPIE.)

Les enzymes des tissus tuberculeux ont été étudiés chez les animaux inoculés dans la cavité pleurale avec le bacille tuberculeux. On remarque la présence des enzymes spéciaux aux leucocytes polynucléaires peu de temps après l'inoculation, mais leur activité diminue très vite. Un deuxième enzyme qui digére le proteïde dans un acide faible est présent en abondance jusqu, à ce que la caséation survienne, mais disparait ensuite. Le sérum de l'exsudation qui s'accumule dans la poitrine perd le pouvoir possédé par le sérum du sang d'arrêter ces enzymes et autres enzymes similaires. L'enzyme qui opère dans l'acide se trouve évidemment présent dans les cellules épitheliales du tubercule et ressemble à celles des larges cellules mononucléaires d'une inflammation exsudate tandis que les cellules épithéliales ressemblent L'autolysis causée par les enzymes dont la marche n'est plus arrêtée; ce qui peut expliquer l'occurrence de la caséation dans le tissu contenant les produits du bacille tuberculeux et pauvrement vascularisé.

Die Rolle der Enzyme bei tuberkulösen Verletzungen.—(OPIE.)

Die Enzyme der tuberkulösen Gewebe sind bei Tieren studiert worden, denen der Tuberkelbazillus in die Pleurahöhle inokuliert worden war. Das den polynukleären Leukozyten eigentümliche Enzym ist kurze Zeit nach der Inokulation vorhanden, verringert sich aber rasch in der Aktivität. Ein zweites Enzym, welches Proteide in einer schwachen Säure verdaut, ist

reichlich vorhanden bis Verkäsung eintritt, aber in der Folge verschwindet es. Das exudative Serum, welches sich im Brustkorbe ansammelt, verliert die Kraft, welche das Blutserum besitzt, dieses und andere Enzyme in ihrem Fortschreiten aufzuhalten. Die Enzyme, welche in der Säure wirken, sind zweifellos in den epithelioiden Zellen des Tuberkels enthalten und sind jenen ähnlich, welche von den grossen mononukleären Zellen eines entzündlichen Exudates kommen, denen die epithelioiden Zellen ähneln.

Autolyse, durch die Enzyme verursacht, kann nicht länger zurückgehalten werden, mag das Vorkommen von Verkäsung in Geweben erklären, die Produkte des Tuberkelbazillus enthalten und in ungenügender Weise mit Blutgefässen versehen sind.

PROPRIÉTÉS HUMORALES DES EXSUDATS TUBERCULEUX (APPLICATIONS DIAGNOSTIQUES ET PRONOSTIQUES).

PAR M. PAUL COURMONT,
Lyon.

Depuis dix ans, nous étudions les propriétés humorales des exsudats et principalement des pleurésies, tuberculeux.[1] Nos conclusions actuelles basées sur l'observation de 200 cas d'exsudats divers portent sur les points suivants.

1. QUANTITÉ DE L'EXSUDAT.

Dans la pleurésie séro-fibrineuse primitive, une grande quantité d'exsudat est plutôt d'un bon pronostic. Le liquide empêche les surfaces de la plèvre couvertes de fausses membranes de frotter l'une contre l'autre (Le Damany). Notre observation (voir Thèse de Pallasse, Lyon, 1905) montre que, sauf le cas de granulie pleurale, les pleurésies séro-fibrineuses à grand épanchement guérissent mieux et plus complètement. Ce fait serait contre les ponctions évacuatrices dont les résultats ne sont pas toujours favorables.

2. COAGULABILITÉ.

Nous enseignons depuis longtemps que la production d'un gros caillot dans l'exsudat pleural, hors de la plèvre, est plutôt d'un pronostic favorable; Jousset (de Paris) a publié également qu'une quantité de fibrine inférieure a 0 gr. 50 par litre est d'un mauvais pronostic. Nous considerons comme d'un pronostic défavorable la *diminution*, puis *la disparition* de la coagulabilité de l'exsudat au cours de ponctions successives.[1]

3. TOXICITÉ-ANAPHYLAXIE.

Nous avons publié en 1900 des expériences montrant que la sérosité des exsudats tuberculeux de l'homme est très toxique sur la lapin en injections intra-veineuses.[3] Dans le même mémoire, nous démontrons la *propriété anaphylactique* pour le cobaye de certains exsudats pleurétiques tuberculeux: des injections tres minimes (1 c.c.), mais répétées, de ces exsudats sous la peau du cobaye, font mourir l'animal avec une dose totale qui n'atteint souvent pas le dixième de la dose totale que peut supporter l'animal si cette dose est injectée en une seule fois. ("Toxicité des exsudats tuberculeux," Archiv. de Pharmacodynamie, vol. vii, p. 283, 1900.) Nous sommes revenus

récemment sur cette question ("Anaphylaxie avec les liquides de pleurésies tuberculeuses," Province médicale, 22 Juin, 1907), montrant que nous avons publié ces expériences en 1900, deux ans avant que M. Richet crée le mot "anaphylaxie" et plusieurs années avant les expériences d'Arthus, Rosenau, etc., sur l'anaphylaxie par le sérum de cheval. Au point de vue pratique, nous ne savons pas si cette anaphylaxie pour le cobaye des exsudats tuberculeux indique que l'homme porteur d'une pleurésie soit anaphylaxié par la résorption de son exsudat.

4. Pouvoir Bactéricide.

Il y a dix ans, nous avons montré[2] que la sérosité des exsudats tuberculeux (pleurésies notamment) est bactéricide "in vitro" pour le bacille de Koch (cultures homogènes) qu'on y ensemence. Il y a là une notion théorique importante et un moyen de pronostic intéressant.[2] (Voir: Paul Courmont: "Action des épanchements des séreuses sur les cultures de bacilles de Koch," Soc. de Biologie, 28 Mai 1898.)

5. Pouvoir Agglutinant.

Nous avons demontré que les exsudats tuberculeux sont aglutinants pour le bacille de Koch en cultures homogènes (1898)[4] et qu'il y a là un moyen de *séro-diagnostic local* faisant le diagnostic de localisation. En effet, la plèvre fabrique elle même des agglutinines, et ne les reçoit pas toutes du sang. L'exsudat pleural peut en effet être plus ou moins agglutinant que le sérum sanguin; il peut même être agglutinant alors que le sérum sanguin ne l'est pas, et réciproquement. L'agglutination par les sérosités pleurales conduit au séro-diagnostic et au séro-pronostic.

(A) Séro-diagnostic.

Le pouvoir agglutinant d'un exsudat vis a vis du bacille de Koch (à partir de 1 pour 5) est un signe a peu près certain de tuberculose, et un moyen de diagnostic excellent. L'absence de pouvoir agglutinant d'un exsudat indique, soit que la pleurésie n'est pas tuberculeuse, soit qu'il s'agit d'une tuberculose grave.

(B) Séro-pronostic.

C'est en effet dans les cas graves de tuberculose pleurale que l'exsudat n'est pas agglutinant ou bien perd cette propriété. Nous avons montré[5] (Voir: Jour. Amer. Med. Assoc., May 19, 1906), par une longue observation de 112 cas de pleurésies tuberculeuses suivies pendant 8 ans: que les pleurésies tuberculeuses dont le liquide est *agglutinant guérissent* 75 per cent.; tandis que celles dont le liquide n'est *pas agglutinant meurent* 73 per cent. Les conclusions précédentes s'appliquent non seulement aux pleurésies mais aux péritonites, aux hydrarthroses. Quant au liquide céphalorachidien des méningites tuberculeuses, *il n'est jamais agglutinant.*

6. Tout ce qui précéde montre que les réactions pathologiques de la plèvre ne sont pas passives, mais *actives*. Les séreuses ne sont pas de simples filtres; elles ont un rôle particulier, elles secrètent les anticorps et jouent un rôle actif dans la defense de l'organisme.[1]

PRINCIPALES REFERENCES.

1. Paul Courmont: Précis de Pathologie générale, collection Testut, Doin editeur, Paris, 1908. (Voir: article séreuse.)
2. Paul Courmont: "Action des épanchements des séreuses sur les cultures liquides de B. de Koch," Société de Biologie, 28 Mai, 1898.
3. Paul Courmont: "Toxicité des exsudats pathologiques des séreuses," Archiv. de Pharmacodynamie, p. 283, 1900. "De l'anaphylaxie avec les liquides de pleurésies tuberculeuses," Société médicale des Hôp. de Lyon, Mai, 1907; Province médicale, 22 Juin, 1907.
4. Paul Courmont: "Séro-diagnostic des épanchements tuberculeux," Congrès de la Tuberculose, Paris, 1898. Société de Biologie, Decembre, 1900. Archiv. de méd. expérimentale, Decembre, 1900.
5. Paul Courmont: "Séro-pronostic des pleurésies tuberculeuses," Congrès de Paris de la Tuberculose, 1905. Jour. Amer. Med. Assoc., May 19, 1906.
6. Landis: "Agglutinat. Studies," Jour. Med. Research, March, 1908.

The Humoral Properties of Tuberculous Exudates: Their Diagnostic and Prognostic Applications.—(P. COURMONT.)

1. In primary sero-fibrinous pleurisy, abundant exudate is of good omen. Except cases of pleural granulia, the pleurisies with large effusion recover completely. Aspiration is unnecessary.

2. The production of a clot in the pleura indicates unfavorable prognosis. A diminishing coagulability of the effusion, as shown in successive punctures, is a bad sign.

3. The exudates of tuberculous pleurisy have an anaphylactic property for the guinea-pig, giving fatal effect to one-tenth of the usual fatal dose of Koch's bacilli. We do not know whether a man incurs a similar anaphylaxis during the resorption of a tuberculous pleural effusion.

4. Tuberculous exudates are bactericidal for Koch's bacillus in vitro.

5. Tuberculous exudates agglutinate Koch's bacilli in homogeneous cultures. Agglutinins are produced in the pleura. They may be present in the effusion, but not in the blood; and vice versâ. These facts are useful in diagnosis and prognosis. Agglutinating power is a sure sign of tuberculosis. Absence of agglutinating power means not tuberculous, or else very grave tuberculosis. Pleurisies without agglutative effusions are 75 per cent. fatal; with agglutinating effusions, 75 per cent. curable. The same is true of peritoneal and joint effusions. The effusion of tuberculous meningitis has no agglutinin.

6. Serous membranes are not passive, but active and productive defenders of the body.

ÉTUDE HISTO-CHIMIQUE ET CYTOLOGIQUE DU CRACHAT TUBERCULEUX.

PAR MM. FERNAND BEZANÇON ET S. I. DE JONG,
Paris.

Si depuis longtemps les phtisiologues ont insisté sur quelques uns des caractères macroscopiques des crachats tuberculeux, si quelques lignes sont consacrées dans les traités classiques à la recherche des fibres élastiques, si, dans ces derniers temps, enfin, on trouve quelques travaux sur la présence de lymphocytes ou d'éosinophiles dans les crachats des tuberculeux, on ne pourrait en trouver nulle part une étude microscopique à la fois cytologique et histo-chimique.

Les histologistes croient en effet volontiers que dans cette excrétion des voies respiratoires les éléments anatomiques sont trop altérés dans leurs formes ou leurs réactions pour que leur étude puisse fournir des résultats utilisables. Dans une série de mémoires * nous nous sommes déjà attachés à montrer que l'opinion qui faisait ainsi du crachat un amas de détritus était une opinion erronée. Nous avons montré que, recueilli dans de bonnes conditions et examiné avec une certaine technique, que nous avons minutieusement fixée, le crachat était en réalité "le miroir fidèle des réactions anatomiques des bronches et des alvéoles pulmonaires." Mais dans des premières recherches nous avions systématiquement laissé de côte l'étude du crachat des tuberculeux, à cause de la complexité des formes évolutives de la tuberculose, et préférant nous rendre compte tout d'abord de l'aspect du crachat dans des réactions aussi nettement définies que la pneumonie, la bronchite aigüe, la congestion pulmonaire chronique, l'oedème aigü des poumons, l'asthme. Ces études antérieures nous permettent d'aborder aujourd'hui avec plus de fruit l'étude des crachats tuberculeux.

Dès l'abord nous devons constater que cette étude ne peut nous servir comme moyen de diagnostic. Le vrai procédé de diagnostic c'est la recherche du bacille de Koch, dont nous avons pu constater la précoce apparition dans les crachats, recherche légèrement discréditée, à tort selon nous, au

* F. Bezançon et S. I. de Jong: "Étude histo-chimique et cytologique du crachat pneumonique," Bulletin de la Soc. médicale des hôpitaux de Paris, séance du 5 juillet, 1907, p. 750. "L'exsudat sero-albumineux, le mucus, et les aspects réticulés muqueux des crachats," *ibid.*, 12 juillet, 1907, p. 805. S. I. de Jong: "Étude histo-chimique et cytologique des crachats," Thèse de Paris, 1907.

profit de l'auscultation. Mais, si l'examen cytologique et histo-chimique du crachat peut rendre des services, c'est précisément, parce que miroir fidèle des réactions anatomiques, son étude pourra nous renseigner sur le degré et la nature des lésions tuberculeuses d'où il provient. Aussi cet examen histo-chimique et cytologique prend un intérêt pronostique, puisqu'il nous donnera des résultats différents suivant les formes évolutives que revêt la tuberculose pulmonaire. Ce n'est donc pas au hasard, mais systématiquement en les classant suivant ces formes évolutives, que nous avons étudié les crachats tuberculeux. Nous résumerons ici les résultats de ces recherches, dont le détail et la discussion seront publiées ultérieurement.

1. Pneumonie caséeuse.

On sait déjà combien est spécial en clinique l'aspect macroscopique du crachat de pneumonie caséeuse, et combien parfois tout au début, il ressemble au crachat pneumonique vrai. L'examen histo-chimique confirme cette impression et il est intéressant, étant données les discussions anciennes sur la part attribuable au processus pneumonique dans la pneumonie caséeuse, de voir combien se ressemblent microscopiquement leurs crachats, au début surtout, naturellement.* Ce qui caractérise le crachat de pneumonie franche, c'est au début, un fond formé par le mélange intime de mucus hyalin et d'un exsudat sero-albumineux; sur ce fond sont semés des globules rouges et quelques éléments cellulaires que nous considérons comme des cellules jeunes de l'endothélium pulmonaire. Les jours suivants les gouttes d'exsudat sero-albumineux diminuent d'importance jusqu'à disparaître après la crise; en revanche les polynucléaires, les cellules pulmonaires jeunes, les macrophages endothéliaux demeurent de plus en plus nombreux, mélangés aux reticulums à réaction muqueuse formés par l'agglomération des dégénérescences cellulaires bronchiques.

Le crachat de pneumonie caséeuse présente également au début des gouttelettes d'exsudat sero-albumineux en quantité considérable, plaquées sur du mucus hyalin, avec de très rares cellules, que leur morphologie permet de considérer comme des cellules endothéliales pulmonaires venues de l'alvéole. Les jours suivants, comme dans la pneumonie, les gouttelettes d'exsudat sero-albumineux diminuent, et les différents types cellulaires dont nous avons parlé apparaissent en grand nombre. Mais à ce moment la similitude cesse entre les crachats de pneumonie franche et de pneumonie caséeuse. Tandis que le crachat de pneumonie franche ressemble vers le huitième ou le dixième jour à un crachat de bronchite ordinaire sauf la note

* Sans pouvoir entrer dan des détails de technique pour lesquels nous renvoyons aux mémoires eités plus haut, nous rappellerons que notre coloration fondamentale est le bleu polyehrome de Unna, après fixation du crachat étalé sur lame à l'aeide chromique. Avec ce colorant, à la lumière artificielle, le mucus est violet rouge, et l'exsudat sero-albumineux apparaît sous forme de grosses gouttes violettes bleues.

spéciale de l'importance des macrophages endothéliens, avec de beaux polynucléaires intacts, dans le crachat de pneumonie caséeuse les divers éléments présentent certains caractères communs à tous les crachats tuberculeux même fraichement recueillis. Tous les éléments cellulaires, leucocytes polynucléaires, cellules pulmonaires jeunes en reminiscence, macrophages endothéliaux, et même aspects réticulés à réaction muqueuse subissent un certain degré de dégénérescence. Les contours des cellules ne sont pas nets, les réseaux sont plus fragmentés, et se colorent moins franchement. Les noyaux sont déformés, et souvent, pour les cellules mono-nuclées, que nous considérons comme des cellules alvéolaires endothéliales, ils sont allongés, étirés et irrégulièrement bossués, rappelant les noyaux des cellules épithélioïdes. Quant aux noyaux des polynucléaires ils sont nettement pycnotiques. Enfin notons que la goutte d'exsudat sero-albumineux persiste avec plus ou moins d'importance traduisant l'activité du processus d'infiltration.

2. Phtisie galopante.

Nous ne voulons pas entrer ici dans des discussions concernant les frontières bien incertaines qui séparent certaines pneumonies caséeuses de certains cas étiquetés phtisie galopante. L'aspect microscopique des crachats varie en tout cas suivant les périodes, ayant tantôt les caractères du crachat de pneumonie caséeuse, tantôt ceux du crachat de ramollissement tuberculeux banal. Dans le crachat, vert foncé, rare, adhérent, purulent de certaines phtisies galopantes avec gros foyers soufflants on n'est pas peu surpris de ne trouver que de rares polynucléaires. Ici ce qui frappe ce sont encore les gouttelettes d'exsudat sero-albumineux, comme dans le crachat de pneumonie franche ou d'oedème aigu du poumon. De plus on trouve beaucoup de cellules alvéolaires. Mais les aspects de dégénérescence dont nous avons parlé au paragraphe précédent sont très accentués. À d'autres moments quand les signes physiques de ramollissement banal dominent, la gouttelette d'exsudat sero-albumineux perd en importance, et le crachat ressemble à celui des malades atteints de tuberculose banale ramollie, dont nous parlerons. C'est seulement dans ce cas ou la fonte du parenchyme est rapide que nous avons pu constater facilement la présence de fibres élastiques. Nous n'avons pas eu besoin d'avoir recours aux procédés compliqués, de dissolution et de centrifugation du crachat, avec examen du culot. Le simple examen des lames colorées par la fuchséline de Weigert et décolorées par l'alcool absolu, suivant le procédé utilisé, en histologie pour la coloration des fibres élastiques, a suffi à nous montrer la présence de ces éléments dans la plupart des cas de phtisie galopante.

3. Forme fibro-caséeuse chronique commune.

Il est extrêmement difficile aujourd'hui avec les idées régnantes de préciser ce qu'on appelle le début de la tuberculose pulmonaire. Au moment

du début véritable, les malades ne crachent pas, et pour les malades qui sont seulement suspects qui crachent, et qui n'ont pas de bacilles, il est très difficile d'affirmer qu'il s'agit de crachats venant de la lésion tuberculeuse. Signalons ici l'intérêt que présente l'examen cytologique des crachats chez quelques tuberculophobes, respirant mal parce que atteints de rhinopharyngite chronique, et ayant un crachat matitunal ayant les caractères microscopiques du crachat pharyngé que nous avons étudiés ailleurs. En réalité chez des tuberculeux pulmonaires vrais, quand nous avons des crachats à examiner, ils présentent déjà le plus souvent un petit point de ramollissement limité.

Dans ces cas de ramollissement tout à fait au début, de lésions tout à fait limitées, nous avons trouvé sur un fond de mucus des polynucléaires présentant déjà un certain degré de pycnose, et de la tendance à la fragmentation, des cellules mononuclées que nous considérons comme des cellules alvéolaires pulmonaires, et beaucoup de cellules endothéliales macrophagiques, grandes cellules à protoplasma basophile vacuolaire, avec un noyau excentrique, renfermant souvent du pigment. Mais il y a là sujet à discussion. Cette discussion nous ne pouvons d'ailleurs ici que l'indiquer. Dans ces derniers temps des auteurs allemands, et notamment Wolff-Eissner, ont signalé dans les crachats tuberculeux la prédominance de lymphocytes. Pour nous ce que l'auteur allemand considère des lymphocytes comprend en réalité des cellules alvéolaires jeunes, des cellules bronchiques de remplacement, des fragments de noyaux pycnotiques de polynucléaires. Nous avons déjà discuté la question des cellules mononuclées des crachats dans nos travaux antérieurs, et surtout dans la thèse de l'un de nous; nous y reviendrons encore dans nos communications ultérieures, avec les détails qu'elle comporte.

Si nous examinons maintenant les crachats des malades présentant des signes de ramollissement avancé allant jusqu'à la caséification, nous trouvons un fond vague et granuleux de mucus altéré sur ce fond à cause de la bronchite concomitante souvent si marquée une grande quantité de reticulums à réaction muqueuse, produits de dégénérescence de la cellule bronchique, mais cette dégénérescence est bien plus marquée que dans les bronchites ordinaires. Les réseaux sont fragmentés, et se colorent mal, d'autant plus mal que les signes cavitaires sont plus marqués. Au milieu de ces réseaux altérés des cellules de tout ordre, alvéolaire, polynucléaires, neutrophiles, mais avec des noyaux pycnotiques, et altérés dans leur protoplasma, qui se colore mal, et qui est mal limité. Avec les colorants appropriés on ne trouve que des traces des granulations leucocytaires.

4. Emphysémato-tuberculeux.

Ce groupe comprend deux types de malades. Les uns ne sont tuberculeux que d'étiologie. Leur tuberculose semble cicatrisée en grande partie, et

leur type clinique est celui des bronchitiques chroniques avec emphysème. Ici on trouve des aspects directement opposés à ceux du type précédent. Leurs crachats ont l'aspect microscopique du crachat de bronchite aiguë. Les polynucléaires bien conservés, à granulations neutrophiles nettement mises en évidence par les colorantes appropriés, sont encerclés par des réseaux muqueux bien colorés, élégants et plus ou moins continus. Par place ils présentent du mucus hyalin, et quelques cellules alvéolaires intactes. D'autres malades sont bien bronchitiques emphysémateux, mais leur tuberculose est en évolution et se traduit par un foyer de ramollissement plus ou moins étendu. Leurs crachats, qui, macroscopiquement, ont le même aspect mucopurulent que ceux du groupe précédent, sont microscopiquement très différents, de par l'altération des cellules et des réseaux que nous avons décrite: altération dans la forme des éléments, pycnoses, fragmentations des noyaux et des réseaux, dislocation et effritement des granulations leucocytaires, parfois totalement disparues. Chez les uns et les autres de ces malades enfin des *hémoptysies* surviennent. Nous avons été frappés à côté des globules rouges de la gouttelette d'exsudat sero-albumineux, due au serum, et des débris de fibrine (dont la nature a été vérifiée par les colorants appropriés) par l'importance de la réaction de polynucléose que présentent ces crachats. Les polynucléaires intacts, avec des noyaux et des granulations en parfait état, se présentent en trop grande abondance pour qu'il s'agisse seulement de polynucléaires appartenant au sang épanché. Il y a là une réaction aiguë et il faut noter comme l'ont signalé Flick, Ravenel et Irwin, la prédominance presque constante du pneumocoque dans ces crachats, fait que nous avons constaté également. Vers la fin de l'hémoptysie, au milieu des réseaux de réaction muqueuse presque aussi serrés que dans les crachats de coqueluche, on trouve de très abondantes cellules endothéliales macrophagiques, chargées de pigment.

Dans ce qui précède nous n'avons pas parlé d'éosinophiles. Contrairement à ce qu'ont annoncé certains auteurs, et notamment Carrière en France, on ne trouve jamais de leucocytes eosinophiles en quantité appréciable dans les crachats des tuberculeux. Comme nous l'avons déjà dit ailleurs, la présence d'éosinophiles vrais dans les crachats, est la signature de l'asthme vrai et des états asthmatiformes des emphysémateux.

Tels sont les principaux aspects du crachat tuberculeux. On remarquera que ces recherches ne nous ont pas révélé une signature microscopique caractèristique de l'affection tuberculeuse, mais qu'elles nous permettent d'être renseignés sur le degré de la tuberculose pulmonaire en évolution, sur là marche et les complications de cette évolution. Ces différences d'aspects suivant les formes confirment d'ailleurs la valeur et l'exactitude de cet examen des crachats, puisque ces résultats sont conformes à la variabilité d'évolution de la tuberculose pulmonaire que la clinique nous enseigne.

Histochemical and Cytological Study of Tuberculous Sputum.—(BEZANÇON AND DE JONG.)

In their study of sputum in the most various forms of tuberculosis the authors were unable to find any characteristic sign of the tuberculous nature of the pulmonary lesion; but they discovered differences in the microscopical appearances of sputa according to the variety and course of the lesion. In caseous pneumonia the appearance is analogous to that of the sputa of frank pneumonia. After a few days the polynuclear leukocytes and the conglomerated network of degenerated cells make their appearance; in addition, the young pulmonary endothelial cells, which resemble mononuclear cells, become more abundant. These elements persist during the course of caseous pneumonia, but present a certain degree of degeneration. This degeneration is particularly marked in the sputum of galloping consumption. It is characterized by pyknosis of the polynuclear leukocytes; exhaustion of the granules and their slight tinctorial affinity; the indefinite outline of the cytoplasm of the pulmonary cells, the nuclei of which become elongated like those of the epithelioid cells: vacuolization when they have become macrophagic; and wasting and fragmentation of the mucous network, due to conglomeration of the degenerated cells. The sero-albuminous exudate is revealed by numerous droplets which can be seen by the method described by the authors during the acute stage of the process; it is not present in the sputum during the stage of cavity formation.

In the ordinary form of chronic pulmonary tuberculosis the pulmonary endothelial cells are abundant and at first well preserved; often they are macrophagic. The elements which are often described as lymphocytes are in reality fragments of densely packed (pyknotic) polynuclear leukocytes, young pulmonary endothelial cells, or substituting bronchial cells. During the period of cavity formation the above-mentioned degenerative features predominate.

In emphysematous tuberculous subjects, in whom the tuberculous process is cicatricial or very slowly progressive, the appearance of ordinary chronic bronchitis, with intact polynuclear leukocytes in well-preserved meshworks, is observed. In emphysematous individuals the degenerative features predominate.

Finally, the authors never found genuine eosinophiles, except in true asthma and in the asthmatic states of emphysematous subjects. Elastic fibers do not possess any significance except in the sputum of galloping consumption.

Estudio Histo-químico y Citológico del Esputo Tuberculoso.—(Drs. Fernand Bezançon y S. I. de Jong.)

En el estudio de las diferentes formas del esputo tuberculoso á los autores les fué imposible encontrar un signo característico que pudiera revelar las lesiones pulmonares; mas ellos descubrieron diferencias en las apariencias microscópicas del esputo con relación á la variedad y el curso de las lesiones. En los casos de la degeneración caseosa, la apariencia es análoga á la del esputo de la neumonía verdadera. Después de pocos días los leucocitos polinucleares y una red de células degeneradas aparecen; en adición á esto, las células jóvenes endoteliales del pulmón, que presentan la apariencia de células mononucleares ó macrófagas, son mas abundantes. Estos elementos permanecen durante el curso de la neumonía caseosa, mas presentan un cierto grado de degeneración. Esta degeneración de los elementos es particularmente marcada en la tuberculosis de progreso rápido; esta está caracterizada por la picnosis de los leucocitos polinucleares; desaparición de los gránulos y su ligera afinidad tintórea; los contornos indefinidos del citoplasma de las células pulmonares, el núcleo de las cuales toma una forma elongada como el de las células epiteliales; degeneración completa de la red mucosa debido a la conglomeración de las células degeneradas. En cuanto a la exudación sero albuminosa, se revela por medio de numerosas gotitas, que pueden ser observadas por el metodo recomendado por los autores, durante el estado agudo del proceso: esta está ausente del esputo durante el estado de la formación de cavidades.

En las formas ordinarias de la tuberculosis pulmonar, las celulas endoteliales del pulmon son abundantes y al principio bien preservadas, con frecuencia estas son macrófagas. Los elementos que por lo regular son descritos como linfocitos son en realidad fragmentos de leucocitos polinucleares, densamente conglomerados (picnotic), células endoteliales jóvenes, ó células bronquiales substitutas. Durante el período de la formación de cavidades, el aspecto de la degeneración, arriba mencionado, predomina.

En las personas con tuberculosis enfisematosa, en las cuales el proceso tuberculoso progresa lentamente, la apariencia de la bronquitis crónica ordinaria, con leucocitos polinucleares en una red bien preservada, son observados. En las personas que tienen enfisema los aspectos de degeneración predominan.

Finalmente los autores nunca encontraron eosinofilos genuinos, excepto en casos de asma vedadera y en el estado asmático de las personas enfisematosas. Fibras elásticas no parecen poseer alguna significación exepto en la tuberculosis de marcha rápida.

SEROLOGISCHE UNTERSUCHUNGEN BEI TUBERKULOSE VON DEN DOKTOREN REITTER UND STOERK.

Von Dr. H. von Schrötter,
Wien.

An der k.k. III. medizinischen Klinik in Wien sind von Seiten der Herren Dr. K. Reitter und Dr. E. Stoerk derzeit Untersuchungen im Gange, die zum Zwecke haben, auf dem Wege der serologischen Untersuchung unser Arsenal diagnostischer Behelfe zur Feststellung der Frühdiagnose der Tuberkulose zu bereichern. Es hat sich nämlich gezeigt, dass im Serum Tuberkulöser u. s. w., vorzugsweise im Frühstadium der Erkrankung, Körper colloidaler Natur auftreten, die auf Zusatz der doppelten Quantität 0.5 prozentig karbolisierter physiol. NaCl-Lösung (bei zwölfstündigem Aufenthalt im Brutofen) ausfallen. Zusatz von Aetherextrakt aus Tuberkelbazillen (Extrakt aus $\frac{1}{2}$ Gramm Bazillen auf 200 cm.^{3} karb. Kochsalzlösung) lässt in einem noch höheren Prozentsatz der Fälle die Ausfallungsreaktion positiv erscheinen. Zum Zwecke der diagnostischen Verwertbarkeit dieser Reaktion müssen gewisse Erkrankungen, die wahrscheinlich von Lipämie begleitet sind (Tumoren in regressiver Metamorphose, Diabetes, manchmal auch Infektionskrankheiten nicht-tuberkulöser Natur,—letztere in einem sehr geringen Prozentsatz der Fälle), ausgeschlossen werden.

Serological Studies by K. Reitter and E. Stoerk.—(Von Schrötter.)

In the Third Medical Clinic in Vienna serological investigations are in progress by Drs. K. Reitter and E. Stoerk, intended to enrich our arsenal of means for the early diagnosis of tuberculosis.

It has been demonstrated that in the serum of tuberculous patients, etc., especially in the early stage of the disease, substances of a colloidal nature appear, which are precipitated by addition of double the amount of 0.5 per cent. carbolized sodium chlorid solution (in the course of twelve hours' stay in the incubator).

The addition of an ethereal extract of tubercle bacilli (extract of one-half gram bacilli in 200 c.c. carbolized salt solution) renders the precipitating

reaction positive in an even higher percentage of cases. In the diagnostic application, of this reaction certain diseases, probably accompanied by lipemia, must be excluded (as tumors in regressive metamorphosis, diabetes, occasionally also infections of non-tuberculous character).

Estudios "Serologicos" por los Drs. K. Reitter y E. Stoerk.— (Von Schrötter.)

En la III Clinica Medica de Viena, estan en progreso las investigaciones serologicas por los Drs. K. Reitter y E. Stoerk las cuales tienen prospectos de enriquecer nuestro material en cuanto al diagnostico prematuro de la tuberculosis.

Se ha demostrado que en el suero de los pacientes tuberculosos, etc., especialmente al principio de la enfermedad, substancias de una naturaleza coloidea, que son precipitables por medio de la adicion de una doble cantidad de un 0.5 per cent. de una solucion de cloruro de sodio carbolizado, en el curso de doce horas en el incubador.

La adicion de un extracto etereo del bacilo de la tuberculosis (extracto de un 0.5 gramos de bacilos en 200 c.c. de una solucion carbolizada de la sal), hace la reaccion de la precipitacion positiva en un gran por ciento de los casos. La aplicacion de esta reaccion en el diagnostico en ciertas enfermedades, probablemente acompañadas de lipemia, deberan ser excluidos (como tumores en una regresiva metamorfosis, ocacionalmente la diabete y tambien otras infecciones de caracter no tuberculoso).

Etudes sérologiques Faites par K. Reitter et E. Stoerk de Vienne.— (Von Schrötter.)

Dans la III^{me} Clinique Médicale à Vienne les docteurs K. Reitter et E. Stoerk sont en train de faire des investigations sérologiques pour enrichir notre arsenal de moyens pour le diagnostic précoce de la tuberculose.

On a démontré que des substances colloïdales se sont montrées dans le sérum des tuberculeux, etc., surtout au commencement de la maladie et qu'elles se précipitent par l'addition de deux fois la quantité de la 0.5 pour cent solution NaCl carbolisée (pendant douze heures dans l'incubateur).

L'addition d'un extrait de tuberculeux bacilles dans de l'éther (extrait d'un demigramme de bacilles dans 200cc. solution NaCl carbolisée) donne une réaction dans une plus grande nombre de cas. Dans l'application diagnostique de cette réaction il faut exclure certaines maladies qui sont probablement accompagnées par la lipèmie (comme les tumeurs en métamorphose rétrograde, le diabète et quelquefois aussi les infections non-tuberculeuses).

INCREASED URINARY CALCIUM EXCRETION IN TUBERCULOSIS:

REMARKS ON ITS PATHOLOGICAL SIGNIFICANCE.

By Alfred C. Croftan, M.D.,
Chicago, Ill.

Scattered through the literature will be found a number of isolated statements referring to an increased excretion of calcium (and magnesium) in the urine of tuberculous subjects. The first of these references that I have been able to find dates back to 1877, when no less an authority than Senator* commits himself in regard to this matter as follows: "It is a positive fact that in pulmonary phthisis an abnormal quantity of calcium is excreted in the urine, even if little food is administered, and if the patients suffer from diarrhea." The last important work is published by Ott,† who arrives at quite conclusive results, all pointing to an increased excretion of lime salts in tuberculosis. In the year following I presented a preliminary report, also referring to the calcium excretion in tuberculosis, before the Pathological Society of Philadelphia,‡ the main points of which are incorporated in this article:

Critique of Urinary Calcium Determinations.

Determinations of the urinary calcium excretion in order to be of value must take into consideration a number of factors. In the first place, it is necessary to distinguish between what may be called the *exogenous* and the *endogenous* urinary calcium excretion, the former comprising that portion of the calcium, introduced with the food, that is promptly assimilated, enters the blood, and thence passes into the urine; the latter, the calcium that is liberated from fixed calcium combinations of the body and, on being thrown into the circulating blood, is promptly excreted in the urine.

In health the latter, endogenous calcium excretion, is essentially a constant factor, and does not fluctuate materially from day to day, varying, however, to some extent in each individual. The former, exogenous calcium excretion, is altogether inconstant, and fluctuates from day to day, inasmuch as it is dependent exclusively upon the amount of calcium ingested,

* Centralb. f. d. inn. med. Wiss., 1877.

† Deutsch. Arch. f. klin. Med., vol. lxx, p. 582, 1901.

‡ Croftan: Proc. Path. Soc., Philadelphia, March 7, 1902; also Jour. Tuberculosis, vol. v, i, January, 1903.

the character of the calcium compounds present in the food, and the assimilability of the latter. Moreover, only a small proportion of the calcium administered by mouth appears in the urine, the bulk being excreted in the feces. Fully 90 to 95 per cent. of calcium salts, for instance, administered by mouth reappear in the feces, the greater portion not being absorbed at all (Voit, Hoppe-Seyler), and, of the small proportion absorbed, a large percentage being carried back to the bowel. Fully 5 to 10 per cent. of the ingested calcium, however, always appears in the urine (Saborow, Riesell, Schetelig).

In studying the effect of any abnormal process (infection, intoxication, metabolic derangement) upon the urinary calcium excretion, the exogenous calcium excretion must first be rendered constant by the administration of the same, weighed and measured quantities of food of known calcium percentage for a considerable period of time; the calcium figures obtained in this way must, however, be interpreted with much conservatism, because the individual value for the endogenous excretion is not mathematically determinable in advance. Here we are forced to utilize as a basis for comparison the average values for the endogenous calcium excretion, as determined in a number of normal individuals.

Such preliminary studies, involving an immense mass of detail that will shortly be published elsewhere (as these data do not properly belong within the narrow frame of this article), give values for the average adult individual endogenous calcium excretion of 0.05–0.07 gm. of CaO in twenty-four hours.

Both the maintenance of the exogenous calcium excretion at a constant level and the preliminary determination of the endogenous calcium excretion* are carried out with much greater facility in animal experiments than in human studies. The greatest care must, of course, be exercised in every case, while feeding with a diet of known constant calcium content, to keep the subjects in a condition of nutritive, especially nitrogenous, equilibrium; as otherwise disintegration of body proteids, abnormal acidulation of the blood-stream (phosphates, sulphates), and presumably dissolution of fixed calcium combinations are brought about, with a resulting abnormal endogenous calcium titer in the urine.

The Calcium Excretion is Increased in Tuberculized Dogs.

The first experiment was made in a dog (See Table I, A) tuberculized with a pure culture of the tubercle bacillus (from the eighth generation of a bacillus derived from a mesenteric gland in a child) injected directly into the jugular vein. The urinary calcium analyses were performed according to the following method:

Take sample of 100 c.c. of urine; evaporate to dryness in the presence of 2 c.c. nitric acid. Add water and nitric acid and evaporate to dryness to decompose carbonaceous matter. The phosphoric acid in the sample should now be in the ortho-form. Add a little water to the residue in the

* Usually so small that it is negligible.

evaporating dish, filter, ignite, and fuse with sodium bicarbonate. Add the mass to the filtrate. Precipitate the phosphorus with silver carbonate; filter. Free the filtrate from silver with hydrochloric acid. Have the solution concentrated and add 50 c.c. ammonium oxalate solution to precipitate the calcium. Dilute to about 500 c.c., bring to boiling, cool, add ammonia, filter, ignite, and weigh the calcium as CaO.

From the time of inoculation to the death of the animal a progressive increase of the calcium excretion was shown, from traces so small that they could not be quantitatively determined to 0.05 the day before the dog's death from general miliary tuberculosis (autopsy finding). The low figure on the nineteenth day cannot be explained. It was probably due to a technical error.

The following table shows similar results, obtained in a series of four other dogs, all corroborating the progressive increase of the urinary calcium excretion in animals kept on a constant diet and artificially tuberculized:

TABLE I.—URINARY CALCIUM EXCRETION IN TUBERCULIZED DOGS.

Dog A.		Dog B.		Dog C.		Dog D.		Dog E.	
Day after Inoculation.	CaO in Grams.	Day after Inoculation.	CaO in Grams.	Day after Inoculation.	CaO in Grams.	Day after Inoculation.	CaO in Grams.	Day after Inoculation.	CaO in Grams.
1	0.0	1	0.0	1	Trace	1	Trace	1	0.0
9	0.0010	10	0.0010	6	0.0021	14	0.0034	12	0.0024
12	0.0078	16	0.0021	21	0.0063	20	0.0102	19	0.0113
14	0.0107	21	0.0093	24	0.0119	29	0.0148	26	0.0196
19	0.0042 (?)	28	0.0142	29	..	31	0.0147	33	0.0248
34	0.0203	38	0.0344	34	0.0294	40	0.0318	40	0.0419
38	0.0510	42	0.0414	35	..	44	0.0309	43	0.0429
39	..	44	..	..	..	45	..	44	..

These results were sufficiently suggestive to warrant the analysis of a number of human tuberculous urines for calcium. The same method of calcium determination was pursued, for the method, while complicated, precludes error and gives absolutely reliable results.

The Calcium Excretion in Tuberculous Subjects.

A summary of the results shows that, in cases of advanced phthisis with destruction of lung tissue, the urinary excretion of calcium is markedly increased, being as high as 0.47 gram of CaO (the normal being 0.2 to 0.3 gram of CaO pro die). This high figure remained constant. In other

cases, examined since then, in which it was possible to place the patients upon a constant diet, the calcium figures were also higher than normal, the excretion fluctuating from 0.37 to 0.41 gram of CaO during the twenty-four hours' period.

Relationship Between Calcium and the Deutero-albumose Accompanying the Tubercle Bacillus.

Interest in the increased urinary calcium excretion in tuberculosis was particularly stimulated by the fact that I had found in previous experimental work that a chemical relationship exists between calcium and an albumose (deutero-albumose) that almost constantly accompanies the tubercle bacillus. This substance has been found in the bodies of the bacilli themselves, and in culture-media in which tubercle bacilli had grown (Kühne, Hahn, Koch, Matthes). Kühne showed that the injection of this deutero-albumose manufactured from bacilli produced a typical rise of temperature in tuberculized animals; Matthes found this albumose in Koch's tuberculin, and discovered it in the urine after tuberculin injections; finally, he succeeded in producing a "tuberculin reaction" with deutero-albumose manufactured from egg-albumen without the intervention of tubercle bacilli. Rouques produced a tuberculin reaction with tuberculous urine, and v. Jaksch found deutero-albumose in such urine. Kossel finally found it in tuberculous sputum, and Matthes in tuberculous lymph-glands and in caseating and calcified tuberculous foci in the lungs.

Moreover, I could show that a peculiar selective affinity exists between calcium and this deutero-albumose, as manifested by the following four observations:

1. In attempting to manufacture some deutero-albumose for the purpose of further experimentation with this interesting body it was found impossible to obtain a product that was altogether free from calcium. It is easy to remove the other inorganic constituents that cling to deutero-albumose, but calcium adheres with great tenacity, so that it cannot be removed by mechanical means (dialysis, precipitation with alcohol, etc.). By chemical means only (ammonium oxalate) can the calcium be removed and a calcium-free albumose be obtained.

2. If a dilute solution of a calcium salt is added to a solution of decalcified deutero-albumose, a definite proportion of the calcium will be bound so tightly that it cannot again be removed by physical means.

3. If two test-tubes are filled with equal quantities of milk, and to one tube is added ordinary deutero-albumose, to the other the decalcified preparation, and rennet is added to both, the curdling of the milk will be considerably retarded in the latter tube. If sufficient decalcified albumose is

added, curdling is inhibited. The calcium of the milk is evidently bound so tightly to the albumose that paracasein calcium (curdle) cannot be formed.

4. If blood is carefully decalcified by the addition of a calculated portion of oxalate, and equal portions of this blood are distributed in a number of tubes, and varying quantities of decalcified deutero-albumose added to each tube, it will be found, on addition of a definite number of drops of a calcium solution to these mixtures, that coagulation is retarded or inhibited in proportion to the quantity of decalcified deutero-albumose added to each tube. Deutero-albumose, therefore, has a greater affinity for calcium than has parathrombin; consequently the formation of calcium parathrombin, *i. e.*, fibrin, is prevented.

Interpretation of Increased Calcium Excretion from the Above.

Having established then two apparently disconnected facts, namely, first, that the urinary calcium excretion is increased in tuberculosis, second, that calcium has a selective affinity for an albuminous product accompanying the tubercle bacillus, the natural inquiry suggested itself whether or not the latter observation could in any way explain the increase in the urinary calcium excretion, and whether any clinical significance attached to these findings. The calcification of tuberculous foci seemed to point out that calcium is commonly found wherever deutero-albumose is formed by the action of the tubercle bacillus.

This problem was approached by comparing the effect of the decalcified and of the calcium-saturated deutero-albumose upon tuberculous animals, and here exceedingly interesting relations were discovered; for, while the pure deutero-albumose possessed very marked fever-producing powers when injected into tuberculous animals, this power was, to a great extent, often altogether, lost when the calcium-saturated product was injected into similar animals.

Through the courtesy of Dr. Leonard Pearson an opportunity was presented to inject calcified deutero-albumose into a herd of twenty cattle that were known to be tuberculous, having reacted to the tuberculin test some months previously. Deutero-albumose prepared from egg-albumen, according to the method of Matthes, and known to produce pyrexia in tuberculous animals, was dissolved in water and saturated with calcium by the addition of a 10 per cent. solution of calcium chlorid. The calcified albumose was precipitated with alcohol, filtered off, and dried. The sediment contained 4.89 per cent. of calcium. Of this product a 5 per cent. watery solution was injected into the above-mentioned herd, and no temperature reaction was obtained, as shown by the following table:

No. of Animal	Temperatures before Injection. Date, February 21st. Time, 6.30.	Temperatures before Injection. Date, February 21st. Time, 8 p. m.	Deutero-albumose Solution	Time of Injection.	Temperatures after Injection. Date, February 22d. Time 2 a. m.	Time 4 a. m.	Time 6 a. m.	Time 8 a. m.	Time 10 a. m.	Time 12 m.
1	101.2	101.4	4 c. c.	8 p.m.	101.2	101.6	101.3	102.	102.4	102.4
2	101.	100.6	4 "	"	100.5	100.6	101.4	101.8	101.9	101.9
3	101.3	101.8	4 "	"	101.	101.	101.3	101.4	102.2	102.6
4	102.2	102.4	4 "	"	102.	102.	102.2	102.1	102.4	102.4
5										
6	102.2	101.6	2 "	"	101.6	101.9	101.8	102.2	102.6	102.2
7	101.6	100.2	2 "	"	101.	101.4	101.4	101.6	101.4	101.
8	102.4	101.2	2 "	"	101.6	101.8	101.6	101.6	102.6	102.9
9	103.2	102.6	2 "	"	102.4	101.6	102.	102.	102.4	102.2
10	101 6	101.1	4 "	"	101.4	101.3	101.4	101.9	102.	102.1
11	100.8	100.8	4 "	"	101.	101.	101.9	102.2	102.6	102.6
12	103.	103.	4 "	"	101.3	100.6	101.6	101.	101.1	101.6
13	101.2	100.6	4 "	"	101.1	101.2	101.4	102.2	101.9	101.8
14	101.1	101.2	5 "	"	101.2	101.1	101.6	102.4	102.4	102.4
15										
16	102.2	102.	5 "	"	101.9	101.4	101.6	102.	101.6	103.
17										
18	100.8	101.6	6 "	"	100.8	101.5	101.8	102.2	101.8	102.2
19	102.	102.1	8 "	"	101.6	100.9	101.2	101.6	102.4	102.2
20	101.	101.5	10 "	"	101.2	101.6	101.	101.6	101.6	101.

Similarly, negative results were obtained in artificially tuberculized dogs and rabbits. The most important conclusion, therefore, that we are apparently justified in formulating, is that the addition of calcium to one of the main, possibly the only, pyretogenic principle manufactured by the tubercle bacillus robs it of its fever-producing power. One is impressed by the idea that this is a disintoxicating process and occurs in the organism wherever deutero-albumose is generated by the tubercle bacillus, thus leading to the deposit of abundant calcium salts *in loco*, and an excessive excretion of calcium in the urine.

Experiments are at present under way to determine whether or not the exhibition of calcium salts, by mouth or by other routes, can in any way modify the temperature movements in tuberculized animals. Some preliminary results that have been obtained give very suggestive figures, but I consider it premature to make any announcement on this subject.

To what extent an increased calcium excretion may be utilized in the early diagnosis of tuberculosis remains to be determined. In view of the difficulty of performing proper quantitative calcium determinations, the inconstancy of the urinary calcium excretion, and the many factors to be considered when interpreting this excretion, the method surely will never be of great practical value. Whether calcium can be used in the treatment

of tuberculosis, particularly with the object in view of controlling the fever movements, remains to be determined.

Métabolisme du Calcium dans la Tuberculose.—(CROFTAN.)

Preuves anciennes et nouvelles, expérimentales et cliniques de l'augmentation de l'excrétion urinaire du calcium dans la tuberculose. Explication de ce phénomène cherchée dans l'affinité par sélection, qu'on trouve entre le calcium et une albumose (deutéro-albumose) presque toujours présente dans les foyers tuberculeux, dans le crachat, les cultures et les média, aussi bien que dans le sang et l'urine de malades tuberculeux et d'animaux rendus tuberculeux. Expériences montrant que cette albumose, quand on en extrait le calcium, possède une grande force pour produire de la fièvre dans les animaux tuberculeux et dans les êtres humains et que cette force pyrogénétique se perd quand l'albumose se combine de nouveau avec le calcium. La combinaison avec le calcium peut donc être considérée comme un moyen protecteur antipyrétique; c'est par cette combinaison qu'on peut expliquer le phénomène particulier de l'augmentation de l'excrétion urinaire du calcium; on peut en tirer aussi certaines conclusions thérapeutiques. Ces conclusions seraient renforcées par l'observation que les ouvriers dans les carrières de sels calcaires semblent posséder une certaine immunité contre l'infection tuberculeuse.

Über den Calcium-Stoffwechsel bei Tuberkulose.—(CROFTAN.)

Vorkommnis alt und neu, experimentell und klinisch einer vermehrten Ausscheidung von Calcium in den Urin bei Tuberkulose. Erklärung dieses Phänomens gesucht in der selectiven Affinität, die als anwesend zwischen Calcium und einer Albumose (Deutero-albumose) gefunden wurde. Nahezu universell anwesend in tuberkulösen Anhäufungen, Sputum, Kulturen und Medien, und im Blute und Urin tuberkulöser Individuen und tuberkulosierter Tiere. Experimente, um zu zeigen, dass diese Albumose, wenn sie von Calcium freigemacht wird, eine besondere fiebererzeugende Kraft bei tuberkulösen Tieren und menschlichen Wesen besitzt, und dass diese fiebererzeugende Kraft verloren geht, wenn die Albumose wieder mit Calcium kombiniert wird. Die Kombination mit Calcium kann daher als ein protektiver, antipyretischer Prozess in der Tuberkulose betrachtet werden, mag in der Erklärung der sonderbaren Erscheinung der vermehrten Excretion von Calcium in den Urin erklärt werden, und legt bestimmte therapeutische Möglichkeiten nahe; die letzteren werden unterstützt durch die Beobachtung, dass Kalksalz-Arbeiter eine gewisse Immunität gegen tuberkulöse Infektion zu besitzen scheinen.

RECHERCHES SUR LE RÔLE DES ACIDES GRAS DU BACILLE TUBERCULEUX.

PAR LES DOCTEURS JEAN CAMUS ET PH. PAGNIEZ,

Paris.

Les travaux de Prudden et Hodenpyl* ceux de Strauss et Gamaleia† ont établi le rôle pathogène des bacilles de Koch tués. Auclair‡ à extrait, par l'éther et le chloroforme certaines substances du bacille tuberculeux qu'il a appelées suivant le solvant employé éthero-bacilline et chloroformo-bacilline.

Dans cette masse de substances graisseuses, cireuses extraites du bacille de Koch et dont Auclair avait montré le pouvoir pathogène, nous avons voulu isoler des substances actives. Celles-ci sont peut être nombreuses, un groupe a surtout attiré notre attention. C'est celui des acides gras.§

Quelques auteurs parmi lesquels Koch, Viquerat‖, Kresling** ont signalé la présence d'acides gras parmi les produits adhérents du bacille tuberculeux. Nos analyses personnelles†† faites avec l'aide de Nicloux nous ont montré dans un échantillon de chloroformo-bacilline d'Auclair la présence de 22.4 pour 100 d'acides gras libres et dans deux échantillons d'ethero-bacilline 50.3 pour 100 d'acides gras libres dans un cas et 20.8 pour 100 dans un autre échantillon.

Les différences qu'on remarque dans la teneur en acides gras de ces différents échantillons peut tenir à bien des causes; à l'âge des cultures, à la durée

* Prudden et Hodenpyl: "Studies on the Action of Dead Bacteria in the Living Body," New York Med. Jour., 1891.

† Strauss et Gamaleia: "Contribution à l'étude du poison tuberculeux," Arch. de med. exper. et d'anat. pathol., 1891, p. 705.

‡ Auclair: "Recherches sur la pneumonie tuberculeuse," Arch. de med. exper., mai, 1899. "Selerose pulmonaire d'origine tuberculeuse," Arch. de med. exper., mars, 1900. "Recherches sur les poisons microbiens. Les poisons microbiens à détermination locale prédominante," Arch. de med. experim., novembre, 1903.

§ Une graisse on le sait est un corps neutre formé par la combinaison d'un ou plusieurs acides gras et de glycérine. Ce sont les acides gras qui établissent par leurs variétés l'individualité de chacune des graisses. Une graisse devient acide quand une partie des acides gras qui la compose devient libre.

‖ Viquerat: "Contribution à l'étude de la tuberculose," Revue med. Suisse romande, xix, 1899. "Beitrag zur Tuberkulin-Frage," Centralbl. f. Bakter., t. xxvi, 1899.

** Kresling: Arch. des Sc. biol. de St. Pétersbourg, t. ix, 1902.

†† Jean Camus et Ph. Pagniez: Soc. de Biol., 4 nov., 1905, C. R. Acad. des Scienees, 6 novembre, 1905. Soc. de Biol., 23 Decembre, 1905.

de dissolution, etc. mais il est bien établi que le bacille de Koch est constitué par une proportion très importante d'acides gras libres.

Quelle est l'importance de des acides gras? Nous résumerons ici nos premiers travaux et nous en apporterons de nouveaux et inédits. L'ensemble de ce mémoire sera divisé en 3 parties:

I. Recherches sur le rôle des acides gras dans la colorabilité spéciale du bacille tuberculeux.

II. Recherches sur les lésions produites par les acides gras.

III. Essai d'immunisation locale à l'aide des acides gras.

I. Recherches sur le Rôle des Acides Gras dans la Colorabilité Speciale du Bacille Tuberculeux.*

Un fait domine les rapports du bacille tuberculeux avec les matières colorantes: c'est son *acido-resistance*. C'est le pouvoir qu'il possède quand il a été imprégné par une couleur d'aniline de résister à la décoloration par les acides forts dilués. La méthode d'Ehrlich, celle de Ziehl sont basées sur l'acido-résistance du bacille.

Etudions d'abord comment les acides gras en général se comportent vis à vis de ces méthodes; nous verrons ensuite les résultats obtenus avec les acides gras du bacille lui-même, et nous montrerons enfin qu'il peut exister d'autres moyens de déceler la présence d'acides gras libres au niveau du bacille tuberculeux.

(*a*) Prenons des acides gras extraits de l'huile de coton ou de l'huile de lin, mettons en une gouttelette au centre d'un petit carré de papier à filtrer, puis traitons ces morceaux de papier comme des préparations de bacilles tuberculeux. Nous verrons qu'avec la méthode de Ziehl et celle d'Ehrlich le centre seul du papier qui a été touché par les acides gras reste coloré à la fin des opérations. Tout le reste des morceaux de papier est décoloré par les acides, les acides gras des huiles de coton et de lin sont donc acido-résistants comme le bacille de Koch.

Nous avons vu que plusieurs acides gras, principalement ceux qui ont un poids moléculaire élevé jouissent de cette propriété d'acido-résistance. Les mêmes recherches faites avec des graisses rigoureusement neutres montrent que celles-ci ne sont pas acido-résistantes. Par contre les vielles huiles devenues rances, ou mieux acides, sont acido-résistantes, grâce aux acides gras qui sont alors en partie libres.

M. Gardenghi† M. Ciaccio‡ ont publié des résultats conformes aux nôtres en ce qui touche aux acides gras.

* Voir Jean Camus et Ph. Pagniez: "Acides gras du bacille tuberculeux," Presse Médicale, 30 Janvier, 1907.

† Gardenghi (de Parme): "La resistenza agli acidi dei grassi colorati con colori d'anilina," Associazione med. chir. di Parma, 1906, 20 Avril, résumé par l'auteur in Auto Riassunti e revista dei lavori Italiani di medicina interna, 1906, vol. iv, No. 5.

‡ Ciaccio: "Sur l'acido-résistance du bacille de Koch," Soc. Biol., 1906, 24 mars.

(*b*) Une démonstration de toute évidence est fournie quand on fait comme nous l'avons indiqué plus haut la dissociation des produits du bacille tuberculeux soluble dans l'éther. Nous avons vu qu'après séparation de ces produits en graisses neutres et acides gras libres, les graisses neutres étaient dépourvues d'acido-résistance, alors que les acides gras du bacille tuberculeux se colorent par les méthodes d'Ehrlich et de Ziehl absolument comme le bacille lui-même. Qu'il existe d'autres substances acido-résistantes dans le bacille, la chose est possible bien que les recherches de Cantacuzène soient peu favorables à cette hypothèse. Cet auteur employant une méthode de dégraissage qui parait irréprochable a noté que les bacilles tuberculeux dégraissés n'étaient plus acido-résistants. Quand on sait que le bacille tuberculeux est constitué en grande partie par des acides gras et que ces corps sont acido-résistants il faute se méfier d'un dégraissage incomplet quand on trouve la propriété acido-résistante du bacille après action de solvants divers. La méthode qu'a employée M. Ciaccio* nous a dans un travail antérieur semblé passible de cette objection.

(*c*) Existe-t-il d'autres moyens de déceler la présence d'acides gras libres au niveau du bacille tuberculeux?

Les acides gras peuvent former avec différents métaux des savons métalliques qui prennent une teinte noire par l'action du sulfhydrate d'ammoniaque. Utilisant cette réaction nous avons pu montrer la présence d'acides gras sur des amas de bacilles tuberculeux provenant de culture, mais cette réaction caractéristique ne se produit pas sur des bacilles isolés. La zone infinitésimale d'acides gras qui se trouve au niveau d'un bacille n'est sans doute pas assez sensible pour que la réaction se produise. Le sous acetate de plomb, le sous acetate de cuivre, l'acetate de fer nous ont permis de réaliser les réactions des savons métalliques sur des amas plus ou moins volumineaux de bacilles tuberculeux.

La méthode que Benda a proposée pour déceler la présence d'acide gras a été adoptée par nous de la façon suivante à la recherche du bacille tuberleux.

1. Dessecher et fixer les bacilles sur une lame de verre comme pour les autres méthodes.

2. Traiter la lame à chaud par une solution de sous acetate de cuivre à saturation (pendant quelques minutes) jusqu'à production de vapeur.

3. Laver à grande eau.

4. Traiter la lame pendant quelques minutes à chaud avec une solution d'hematoxyline à 1% (coloration très forte).

5. Decolorer par une solution étendue de ferrycyanure de potassium et de borax.

Les bacilles tuberculeux apparaissent alors colorés en bleu, les uns en bleu pâle, les autres en bleu noir.

* Ciaccio: *loc. cit.*

Cette méthode permet de trouver des bacilles tuberculeux dans des crachats mais d'autres microbes que le bacille de Koch donnent une réaction semblable. Il est possible que ce procédé ne soit pas spécifique pour les acides gras, ou que plusieurs variétés de microbes possèdent ces acides. Dans cet ordre d'idée rappelons qu'Auclair a extrait de plusieurs microbes des produits nocifs par l'ether et par le chloroforme; ces extraits renferment peut être des acides gras.

Il est en tous les cas intéressant de mentionner un fait déjà connu et que nous avons observé aussi. C'est que dans une même culture tous les bacilles ne se comportent pas d'une manière identique en face des substances colorantes qui peuvent les imprégner. Il est probable que les bacilles anciens sont plus riches en acides gras que les jeunes, ceci expliquerait pourquoi dans une culture en voile les bacilles de la periphérie sont encore peu acido-résistants.

II. Recherches sur les Lésions Produites par les Acides Gras.*

Sachant par nos analyses qu'on trouve dans le bacille tuberculeux des acides gras libres et des graisses neutres, sachant d'autre part que l'introduction dans les tissus de différentes graisses neutres ne provoque pas de lésions; il était logique de penser qu'une partie au moins des accidents causés par l'injection d'ethero-bacilline ou de chloroformo-bacilline d'Auclair étaient dûs à des acides gras. Les expériences sont venues confirmer cette manière de voir, mais il est difficile d'opérer avec les acides gras du bacille tuberculeux lui-meme dont on ne peut se procurer que des quantités peu importantes.

Nous avons préfére expérimenter d'abord avec des acides gras d'huiles végétales qu'il est facile de se procurer opérant ainsi nous pouvions apprendre si ces acides donnent des lésions comparables à celles de la tuberculose et savoir si ces derniéres sont spécifiques, c'est à dire reproductibles uniquement par le bacille de Koch. Ces deux points étaient intéressants à étudier. Nous avons expérimenté sur le lapin et sur le chien et nos recherches ont porté presqu'uniquement sur les poumons; les acides gras ont été introduits dans ces organes (a) par voie tracheale (b) par voie sanguine.

(*a*) *Introduction d'acides gras dans le poumon par la trachee.*—Souvent des huiles neutres ont été injectées sans aucun inconvénient, dans un but thérapeutique dans le larynx et dans la trachée il n'en est pas de même edes acides gras.

Ceux-ci injectés en grande quantité (quelques centimètres cubes) provoquent rapidement de la congestion oedemateuse diffuse des poumons et entraine la mort par asphyxie.

L'injection de doses plus faibles donne d'abord fréquemment chez le chien des symptômes cliniques intéressants: de la toux répetée des hémo-

* Voir Jean Camus et Ph. Pagniez: "Lésions determinées dans le poumon par les acides gras (considération sur la non specificité des lésions tuberculeuses)," Journal de Physiologie et de pathologie générale, Mai, 1906.

ptysies, des signes d'hépatisation pulmonaire constatables par la percussion et l'auscultation. Ces animaux n'ont pas de fièvre et conservent un bon état général, le processus est purement local. Les lésions constatées à l'autopsie varient suivant l'époque à laquelle on sacrifice l'animal. Quand elles sont récentes elles constituent une congestion hemorragique, splenisation, hépatisation véritable. Plus anciennes, elles se cantonnent, elle sont par places ulcéreuses, par place d'aspect caséeux. Quand ces lésions sont corticules elles peuvent donner de la pleurésie avec épanchement. Histologiquement on note dans les cas récents des lésions d'hépatisation avec réseau fibrineux intra-alvéolaire, des lèsions de nécrose et des hémorragies interstitielles. Dans les cas un peu plus anciens l'endothélium et le tissu conjonctif ont réagi et sont apparues des grandes cellules géantes en plasmodes, tandis que par place on voit une substance amorphe résultat d'une nécrose de coagulation analogue à la caséfication. Plus tard encore le tissu conjonctif a proliféré énergiquement, les cavités alvéolaires sont plus ou moins comblées, les bronches rétrécies par places, dilatées et transformées en cavités kystiques en d'autres points. De temps en temps dans nos lésions nous avons trouvé des follicules très nets avec cellules géantes au centre. Parmi les altérations observées les unes rappellent assez bien celles de la tuberculose, les autres en sont distinctes.

(*b*) *Introduction d'acides gras dans le poumon par voie sanguine.*—L'injection des substances grasses dans les veines provoque la mort disent les classiques, par embolies graisseuses. Quelques uns de nos chiens sont morts en effet immédiatement ou quelques heures après l'injection d'acides gras dans les veines mais un grand nombre d'entre eux n'ont présenté aucun accident immédiat après l'injection dans la veine saphène de 1 gr. et 1 gr. 50 d'acides gras de l'huile de coton ou de l'huile de lin.

Dans le cas d'accidents rapides; une dyspnée intense apparait après l'injection, un liquide rosé, spumeux s'écoule par les narines et l'animal succombe à une congestion oedémateuse très étendue des 2 poumons. Le plus ordinairement on n'observe pas d'accidents immédiats, mais après 24 ou 36 heures on note un peu de toux et de dyspnée et les chiens survivent après ces troubles.

Sacrifiés au bout de 3 ou 4 jours on constate chez certains d'entre eux des granulations pulmonaires peu nombreuses surtout sous pleurales, grisâtres, translucides, variant de la grosseur d'une tête d'épingle à celle d'un pois. Histologiquement ces granulations sont constituées au centre par un vaisseau dont la lumière est remplie de leucocytes polynucleaires de cellules rondes et où l'on peut trouver également une cellule géante. La paroi vasculaire est rompue et un épais manchon de cellules est formé autour du vaisseau, l'ensemble constituant une lésion nodulaire très nette.

Si les lésions sont plus anciennes on voit surtout une prolifération de tissus conjonctif.

Autant qu'on peut conclure de quelques expériences il nous a semblé que l'acide palmitique donnait surtout des lésions congestives et hemorragiques l'acide laurique surtout des lésions de sclérose (ces deux derniers ont été signalés au niveau du bacille tuberculeux) et l'acide butyrique des lésions de desquamation epithéliale et de la diapedèse.

Les coupes au microtome à congélation avec coloration au Scarlach montrent trois jours après l'injection intra-veineuse d'acides gras des vaisseaux obstrués de caillots et à leur voisinage des alvéoles pulmonaires remplis de globules rouges et de nombreuses cellules bourrées de granulations colorées en rouge par le Scarlach. Ces cellules rondes ou allongées sont contenues les unes dans la paroi alvéolaire, les autres insinuées entre les cellules de l'epithelium bronchique d'autres enfin libres dans les cavités alvéolaires. Il est probable qu'il s'agit de phagocytes chargés de particules d'acides gras qui seraient éliminés ainsi en partie par voie aérienne.

Parmi les lésions obtenues par voie trachéale et par voie sanguine les unes sont analogues à celles que donne le bacille tuberculeux et prouvent que celui-ci n'agit pas d'une manière absolument spécifique, d'autres lésions sont différentes et ceci n'a pas lieu de nous surprendre. En effet nous nous sommes servis d'autres acides gras que ceux du bacille tuberculeux et il est probable que ces derniers employés purs donneraient des lésions plus typiques. Cependant nous ne croyons pas qu'ils provoqueraient des altérations identiques à celles du bacille lui-même. Le microbe de Koch vivant dans les tissus agit à la fois par tous les produits qui résultent de sa nutrition propre, il doit pour ainsi dire distiller ces produits lentement et d'une façon continue et les cellules de l'organisme en face de ces germes actifs ne doivent pas se comporter de la même manière qu'en face d'une masse inerte d'acides gras qui est introduite brutalement dans le poumon.

Un fait néanmoins est certain, c'est que les acides gras sont nocifs pour les tissus animaux et que le bacille tuberculeux en détient une forte proportion il est logique de penser qu'il les utilise dans la production des lésions qu'il détermine.

III. Essai D'immunisation Contre les Acides Gras et par eux Contre le Bacille Tuberculeux.

Ayant constaté les importants désordres causés dans les tissus par les acides gras, considérant d'autre part que ce sont des poisons locaux adhérents aux bacilles nous avons pensé que peut être on pourrait parvenir à habituer les cellules de l'organisme à réagir à se défendre contre eux. Notre plan n'était pas de créer une immunité générale contre la tuberculose, nos ambitions étaient bien moindres, nous voulions seulement entrainer peu à peu un organe ou plutôt une région à lutter contre les acides gras et par là même dans une certaine mesure contre le bacille tuberculeux. Nous nous sommes

adressés au péritoine. Nous indiquerons les effets des injections d'acides gras dans le péritoine avant d'exposer notre tentative d'immunisation.

Lapin Poids = 1800 gr.:

2 Avril, on lui injecte dans l'abdomen 1 gr. 50 d'acides gras de l'huile de coton.

3 Avril, P = 1940 gr. très bon aspect.
5 Avril, P = 2060 gr.
20 Avril, P = 2390 gr.
30 Avril, P = 2220 gr.

1 Mai, on le trouve mort. La surface du gros intestin est couverte de grumeaux, d'un enduit visqueux, le foie et la rate sont englobés dans de vastes fausses membranes qui l'enlèvent par lambeaux. Le péritoine est infiltré de sérosité—Il existe un épanchement dans la plève droite, le poumon droit est très congestionné.

Lapin Poids = 1670 gr.:

12 Avril, injection dans le péritoine de 1 gr. 50 d'acides gras de l'huile de coton.

13 Avril, il meurt dans la soirée. L'abdomen est très ballonné, les anses intestinales distendues; léger épanchement rosé dans le péritoine. Epiploon retracté rempli de détritus gris blanchâtres; le foie est également recouvert de fausses membranes.

Lapin Poids = 2 k. 350 gr.:

18 Avril, injection intra-péritonéale de 1 gr. 50 d'acides gras de l'huile de coton.

19 Avril, P = 2 k. 240 gr. on trouve à la palpation abdominale plusieurs masses dure du volume d'une noix.

30 Avril, P = 2 k. 330 gr. on ne trouve plus rien à la palpation de l'abdomen.

7 Mai, P = 2 k. 650 gr. injection intra-péritonéale de 5 c.c. d'un mélange:

Acides gras	5 gr.
Huile de coton	15 gr.

11 Mai, P = 2 k. 780 gr. injection de 1 gr. 50 d'acides gras de coton.

13 Mai, Mort-péritonite avec adhérences multiples débris jaunâtres à la surface des anses d'intestins—Conjestion diffuse des deux poumons.

Cobaye Poids = 650 gr.:

12 Novembre, injection dans le péritoine de 2 c.c. du mélange suivant:

Acides gras du coton	5 gr.
Acide laurique	0 gr. 20
Acide palmitique	0 gr. 20
Eau distillée	10 gr.

15 Novembre Mort—Fausses membranes sur les faces inférieure et supérieure du foie, lésions du grand épiploon, qui est très rétracté.

Cobaye Poids = 770 gr.:

12 Novembre, même injection intrapéritoneale qu'au cobaye précédent.

15 Novembre, mort avec les mêmes lésions surtout marquées dans le grand épiploon.

Deux autres cobayes survivent à la même injection intrapéritoneale.

COBAYE POIDS = 630 GR.:

19 Octobre, injection intrapéritoneale de 1 c.c. du mélange suivant:

Acides gras du coton..... 2 gr.
Huile de coton.....10 gr.

22 Octobre, P = 640 gr. Injection de 1 c.c. du mélange suivant:

Acide gras du coton.....3 gr.
Huile de coton.....6 gr.
Acide laurique.....0 gr. 10
Acide palmitique.....0 gr. 10

27 Octobre, P = 645 gr.

3 Novembre, P = 660 gr. Injection de 1 c.c. du mélange suivant:

Acide gras du coton.....4 gr.
Huile de coton.....4 gr.
Acide laurique.....0 gr. 20
Acide palmitique.....0 gr. 20

12 Novembre, P = 700 gr. Injection de 2 c.c. du mélange suivant bien émulsionné:

Acides gras du coton..... 5 gr.
Acide laurique..... 0 gr. 20 centig.
Acide palmitique..... 0 gr. 20
Eau distillée.....10 gr.

14 Novembre, mort—péritonite étendue mais surtout marquée au niveau du grand épiploon et du foie.

COBAYE P = 700 GR.:

10 Octobre, injection intrapéritoneale de 1 c.c. du mélange suivant:

Acides gras du coton..... 1 gr.
Huile de coton.....15 gr.

15 Octobre, P = 710 gr. injection 1 c.c. du mélange suivant:

Acides gras du coton.....1 gr.
Huile de coton.....8 gr.

19 Octobre, P = 710 gr.

22 Octobre, P = 735 gr. injection de 1 c.c. du mélange suivant:

Acides gras du coton.....3 gr.
Huile de coton.....6 gr.
Acide laurique.....0 gr. 10
Acide palmitique.....0.10

27 Octobre, P = 560 gr.

29 Octobre, Mort, péritonite généralisée avec zones de péritonite enkystée.

Nous pourrions multiplier les exemples ayant répété les injections analogues sur un grand nombre d'animaux. On voit par les exemples ci-dessus combien le péritoine est sensible à de petites doses d'acides gras et quelles lésions importantes ces acides déterminent. On voit aussi que les réactions sont très inégales avec les mêmes doses chez des animaux de même espèce. Certains cobayes meurent très rapidement en 24 ou 48 heures après une injection intra péritoneale d'acides gras alors que d'autres avec la même injection meurent seulement au bout de plusieurs jours et que d'autres résistent.

Nous ne sommes pas parvenus à immuniser d'une façon régulière et certaine le péritoine de nos animaux contre les acides gras.

Cet essai d'immunisation ayant échoué nous avons voulu voir si en injectant à plusieurs reprises de petites quantités d'acides gras dans le péritoine de cobayes, cette séreuse deviendrait plus résistante vis à vis des bacilles tuberculeux ceux-ci comme nous l'avons montré étant constitués en partie par des acides gras, et dans ce but nous avons injecté différents acides entre autres l'acide palmitique et l'acide laurique qui ont été signalés au niveau du bacille tuberculeux.

Cobaye P = 450 gr.:

16 Novembre, injection intrapérit. de 1 c.c. du mélange suivant:

Acide laurique	0 gr. 10
Acide palmitique	0.10
Acides gras du coton	0.20
Huile de coton	0.20
Eau	5 gr.

21 Novembre, P = 460 gr. Injec. de 1 c.c. du mélange suivant:

Acide laurique	0 gr. 10
Acide palmitique	0 gr. 10
Acides gras du coton	0 gr. 70
Huile de coton	0.20
Eau	12 gr.

28 Novembre, P = 495 gr. Injection de 1 c.c. de mélange suivant:

Acide laurique	0 gr. 10
Acide palmitique	0 gr. 10
Acides gras du coton	1 gr.
Huile de coton	0 gr. 20
Eau	10 gr.

10 Decembre, P = 560 gr. Injection de 2 c.c. du mélange suivant:

Acide laurique	0 gr. 10
Acide palmitique	0 gr. 20
Acides gras du coton	2 gr.
Huile de coton	0 gr. 40
Eau	15 gr.

14 Decembre, P = 520 gr.

17 Decembre, P = 550 gr. Injection intrapéritonéale de 1 c.c. d'une emulsion concentrée de bacille tuberculeux virulents.

24 Decembre, P = 490 gr.

2 Janvier, P = 470 gr.

9 Janvier, P = 450 gr.

17 Janvier, P = 595 gr. Abdomen distendu par beaucoup d'ascite.

19 Janvier, mort; ascite colossale, tuberculose du foie, du péritoine, rate grosse, granulations dans le poumon.

Cobaye P = 380 gr.:

16 Novembre, injection de 1 c.c. $\frac{1}{2}$ même mélange que cobaye précédent.
21 Novembre, P = 390 gr. Injection " " "
28 Novembre, P = 410 gr. " 1 c.c. " "
10 Decembre, P = 470 gr. " 2 c.c. " "
14 Decembre, P = 465 gr.

17 Decembre, P = 490 gr. Inoculation intraperitonéale de 1 c.c. de la même émulsion de bacilles tubere. que ci-dessus.
24 Decembre, P = 520 gr.
2 Janvier, P = 580 gr.
9 Janvier, P = 655 gr.
17 Janvier, P = 700 gr.
11 Avril, mort; ascite hémorragique; foie enorme rempli de lésions tuberculeuses étendues; pleurésie hémorragique peu abondante, tuberculose pulmonaire nette mais discrète.

COBAYE P = 510 GR.:
21 Novembre, même injection que cobaye ci-dessus.
28 Novembre, P = 545 gr. "
10 Decembre, P = 580 gr. "
14 Decembre, P = 595 gr.
17 Decembre, P = 590 gr. Inoculation intrapéritonéale de 1 c.c. de même émulsion de bacilles tuberculeux que ci-dessus.
24 Decembre, P = 575 gr.
2 Janvier, P = 550 gr.
9 Janvier, P = 460 gr.
17 Janvier, P = 445 gr.
23 Janvier, mort; ascite considérable, tuberculose énorme du foie et de la rate (rate très volumineuse) tuberculose nette mais discrète des poumons.

COBAYE P = 500 GR.:
21 Novembre, même injection que cobaye ci-dessus.
28 Novembre, P = 530 gr. "
10 Decembre, P = 570 gr. "
14 Decembre, P = 580 gr.
17 Decembre, P = 550 gr. Inoculation intrapéritonéale de même émulsion de bacilles tuberculeux que ci-dessus.
24 Decembre, P = 520 gr.
2 Janvier, P = 515 gr.
9 Janvier, P = 470 gr.
17 Janvier, P = 520 gr.
25 Janvier, mort; grosse tuberculose du foie, rate énorme ascite tuberculose pulmonaire nette.

COBAYE P = 815 GR.:
2 Novembre, injection intraperitonéale de 1 c.c. de mélange suivant:

Acides gras du coton	4 gr.
Huile de coton	4 gr.
Acide laurique	0 gr. 20 centig.
Acide palmitique	0 gr. 20 centig.

12 Novembre, P = 660 injection de 2 c.c. du mélange suivant:

Acides gras du coton	5 gr.
Acide laurique	0 gr. 20
Acide palmitique	0 gr. 20
Eau distillée	10 gr.

21 Novembre, P = 620 gr. Injection du même mélange que les cobayes cidessus à la même date.
28 Novembre, P = 625 gr. "
10 Decembre, P = 720 gr. "
14 Decembre, P = 665 gr.
17 Decembre, P = 705 gr. Inoculation intrapéritonéale de 1 c.c. de même émulsion de bacilles tuberculeux que ci-dessus.
24 Decembre, P = 590 gr.
1 Janvier, P = 530 gr.
9 Janvier, P = 520 gr.
17 Janvier, P = 540 gr.
30 Janvier, mort; grosses masses jaunes caséeuses dans l'abdomen au niveau du grand epiploon, du mésentère et du péritoine pariétal, tubercules discrets du foie et de la rate, adhérences des anses intestinales, tuberculose nette mais récente des poumons, les lésions abdominales sont manifestement plus importantes et plus anciennes.

Cobaye Poids = 640 gr.:
12 Novembre, injections intrapéritonéales de 2 c.c. du même mélange que le précédent.
21 Novembre, P = 480 gr. "
28 Novembre, P = 450 gr. "
10 Decembre, P = 495 gr. "
17 Decembre P = 505 gr. Injection intrapéritonéale de 1 c.c. de même émulsion de bacilles tuberculeux que les précédents:
24 Decembre, P = 520 gr.
1 Janvier, P = 630 gr.
9 Janvier, P = 615 gr.
17 Janvier, P = 660 gr.
11 Avril, P = 880 gr.
30 Juli, P = 850 gr. On sent de grosses masses ganglionnaires probablement tuberculeuses au niveau des plis inguinaux; il succombe pendant la période des vacances 9 mois environ après l'inoculation, on ne peut pratiquer son autopsie.

Les cobayes suivants servent de témoins à ceux du groupe précédent. On leur injecte dans le péritoine le 17 Decembre c'est à dire le même jour la même quantité de la même émulsion de bacilles tuberculeux.

Cobaye P = 590 gr.:
17 Decembre, inoculation intrapéritonéale de l'émulsion de bacilles tuberculeux.
24 Decembre, P = 605 gr.
2 Janvier, P = 655 gr.
9 Janvier, P = 670 gr.
17 Janvier, P = 670 gr.
11 Avril, P = 700 gr. Dyspnée très marquée.
13 Avril, mort; poumons très remplis de lésions tuberculeuses, grosses lésions tuberculeuses du foie et de la rate, un peu d'ascite séreuse.

Cobaye P = 500 gr.:
17 Decembre, inoculation intrapéritonéale de l'émulsion de bacilles tuberculeux.

24 Decembre, P = 530 gr.
2 Janvier, P = 585 gr.
9 Janvier, P = 585 gr.
17 Janvier, P = 575 gr.
29 Janvier, mort; grand epanchement sero-sanguinolent dans les plèvres, énorme tuberculose pulmonaire péritoine sain, pas d'ascite, pas de tuberculose de la rate ni du foie, quelques petites lésions dans le grand epiploon.

Cobaye P = 500 gr.:
17 Decembre, inoculation intrapéritonéale de l'emulsion de bacilles tuberculeux.
24 Decembre, P = 540 gr.
2 Janvier, P = 565 gr.
9 Janvier, P = 510 gr.
17 Janvier, P = 515 gr.
10 Fevrier, mort; tuberculose très étendue des 2 poumons, pas d'ascite, petites taches discrètes à la surface du foie, rate un peu hypertrophiée, quelques noyaux crétacés et caséeux au centre dans le grand épiploon.

Cobaye P = 570 gr.:
17 Decembre, inoculation intrapéritonéale de l'émulsion de bacilles tuberculeux.
24 Decembre, P = 585 gr.
2 Janvier, P = 645 gr.
9 Janvier, P = 635 gr.
17 Janvier, P = 650 gr.
11 Avril, P = 675 gr.
16 Avril, mort; grosses lésions tuberculeuses des deux poumons, pas d'ascite, mais lésions tuberculeuses du foie et de la rate à peu près de même importance que celles des poumons.

Cobayes P = 620 gr.:
17 Decembre, inoculation intrapéritonéale de l'émulsion de bacilles tuberculeux.
24 Decembre, P = 610 gr.
2 Janvier, P = 620 gr.
9 Janvier, P = 535 gr.
17 Janvier, P = 465 gr.
1 Fevrier, mort; très grosses lésions tuberculeuses des deux poumons, tubercules jaunes confluents—abondante ascite lactescente; lésions très discrètes du foie—noyaux calcaires à la périphérie et caséeux au centre dans le grand épiploon—rate hypertrophiée sans tubercule.

Cobaye P = 555 gr.:
17 Decembre, inoculation intrapéritonéale de l'émulsion de bacilles tuberculeux.
24 Decembre, P = 550 gr.
2 Janvier, P = 630 gr.
9 Janvier, P = 650 gr.
17 Janvier, P = 650 gr.
11 Avril, P = 790 gr.
14 Mai, mort; ascite hemorragique considérable—Foie énorme tubercu-

leux, grosse rate avec peu de lésions tuberculeuses. Adenopathie trachéo-bronchique—tuberculose discrète et récente des poumons.

L'examen des faits précedents montre que nous avons échoué complètement dans nos tentatives d'immunisation contre la tuberculose à l'aide des acides gras. Un de nos cobayes a bien survécu 9 mois à l'inoculation tuberculeuse ce qui pourrait indiquer une certaine résistance, mais nous ne pouvons faire fond sur ce cas isolé.

Il était logique de faire ces essais et c'est pourquoi nous avons voulu compléter ainsi la série de nos recherches sur les acides gras.

Peut-être se demandera-t-on pourquoi nous avons tenu à publier des résultats négatifs, c'est que dans une question comme celle de la lutte contre la tuberculose toutes les recherches patientes et rationnelles méritent de voir le jour. En attendant des faits positifs, nets et indiscutables il n'est peut-être pas sans intéret d'esposer de temps en temps très modestement des essais négatifs.

D'ailleurs nos faits sont instructifs par eux-mêmes; si l'on se donne la peine de comparer les lésions trouvées à l'autopsie des cobayes témoins et celles que nous avons rencontrées chez les cobayes traités par les acides gras on est frappé chez la majorité de ces derniers de la grande prédominance des lésions abdominales et du peu d'importance des lésions thoraciques. C'est précisément le contraire que nous avons observé chez la majorité des cobayes témoins. Nous avons évidemment par les injections antérieures d'acides gras modifié la réceptivité du péritoine pour les bacilles tuberculeux. Il semble que la lutte se soit alors cantonnée avec prédominance dans l'abdomen, et l'on peut discuter sur la question de savoir si nous avons transformé l'abdomen en un lieu de moindre résistance permettant à la tuberculose de s'y développer mieux ou bien si nous avons excité les moyens de défense de la séreuse, exagèré, adapté la phagocytose, assez pour arrêter les bacilles mais pas assez pour les détruire.

La défense de l'organisme contre les acides gras ne résoudrait sans doute pas la question de l'immunisation anti-tuberculeuse qui nous apparait fort complexe, mais il est certain que ces acides gras sont nocifs pour les tissus et que si l'organisme ne solubilise pas, ne neutralise pas cette enveloppe graisseuse il luttera mal contre le bacille; si au contraire les acides gras sont détruits, un des moyens d'action du bacille aura été supprimé, il aura déjà subi un commencement de désorganisation, ce ne sera peut-être pas toute l'immunité, mais une immunité partielle, si l'on veut, par morcellement.

Ceci est possible mais n'est pas démontré, ce que nous croyons avoir établi par ce travail c'est le rôle des acides gras dans la colorabilité du bacille et leur action importante dans la production des lésions.

DIFFICULTÉS DE CONSTATATION ET DE RECHERCHE DU BACILLE TUBERCULEUX DANS LES LÉSIONS TUBERCULEUSES DU FOIE; RÔLE POSSIBLE DU GLYCOGÈNE.

Par Dr. Pièrre Teissier,
Paris.

Pour être electif le rôle défensif du foie à l'égard d'agents infectieux multiples ou de multiples poisons compte parmi les plus importants; les processus que le déterminent sont sans doute divers et complexes. On a marqué la phagocytose (Wengo, Calmette) les propriétés antiseptiques, variables il est vrai, de la bile (Lavereau Nette) la fonction glycogènique. Les données relatives à l'action du glycogène sont parmi les plus précises; la cellule hépatique perd la propriété de fixer le sucre, d'arrêter les poisons, d'attenuer ou de détruire les microbes quand elle ne contient plus de glycogène; son pouvoir est proportionnel à la quantité de glycogène qu'elle renferme.

En 1899, j'ai contribué par des expériences dont les conclusions ont été confirmées depuis à Montier, que le glycogène pur, mélangé en proportions relativement faibles (0.50 centig. à 4 gr. %) à des milieux de culture ou à de l'eau distillée sterilisée, exercait "in vitro" sur certains microbes et poisons un pouvoir attenuant et bactéricide ou antitoxique des plus nets. Nous avons cru pouvoir conclure, entre autres dès ce moment que le glycogène, pouvait expliquer la stérilisation progressive et souvent rapide des grands abcès du foie.

J'ai recherché alors si son action ne pourrait être également marquée pour l'interpretation de ce fait généralement admis, de la difficulté de coloration ou de constatation du bacillus tuberculeux, dans un grand nombre de lésions tuberculeuses hépatiques. Je dis un grand nombre; car s'il est vrai que les tuberculoses à développement rapide or lors de septicémie tuberculeuse, les bacilles, à la périphérie tout au moins, sont nombreux et vivaces, ils peuvent faire défaut ou être très clairsemés et alterés non seulement dans les tubercules fibreux, les procés des cavernes, la membrane limitante des abcés, mais aussi dans les lésions, qui par un développement plus lent, ont acquis la structure folliculaire achevée. Il semble comme on l'a dit que les tubercules du foie soient histologiquement et bactériologiquement comparables aux tubercules du lupus.

Les expériences que j'ai réalisées dès 1849 et de nouveau ces derniers temps ont eu pour but de mettre en contact pendant un temps variable (quelques jours à plus d'un mois) du bacillus tuberculeux humain avec des solutions de glycogène (dans la proportion de 0.20 centig. à 0.40 centig. pour 10 cc. d'eau stérilisée); ces solutions étaient stérilisées à 110° pendant 20 minutes. La culture mère du bacillus tuberculeux m'avait été donnée par le Docteur Benaud le l'Institut Pasteur, comme une culture très virulente; des preparations faites par moi montrèrent constamment un bacille de forme, de dimensions normales, parfaitement coloré et non granuleux.

Le bacille tuberculeux fut incorporé (en amas plus ou moins petits dont quelques uns purent être dissociés par agitation) dans une série de tubes à essai contenant la solution de glycogène. (b) dans une série de tubes témoins renfermant de l'eau distillée sterilisée. Dans ma pensée l'addition de ces tubes témoins était motivée par la necessité de savoir dans le cas de modification constatés sur le bacille tuberculeux ayant séjourné dans les solutions de glycogène, si ces modifications ne suivent pas dus simplement à la vie du bacillus dans la profondeur d'une solution aqueuse.

Chaque série de tubes fut divisée en deux parties, les uns pour être placés à l'étuve à 37°, les autres à la température du laboratoire 22° 25° a l'abri de la lumière.

Tout les quatre jours environ pendant plus d'un mois des préparations étaient faites du bacille de la culture originelle du bacille maintenu en solution glycogénique ou dans l'eau distillée, par la méthode de Ziehl et dans les conditions suivantes: 5 minutes de coloration par la solution de Ziehl partée à l'ebullition —lavage—décoloration soit par l'acide azotique au $\frac{1}{3}$ ou l'acide sulfurique au $\frac{1}{4}$ pendant 1 minute $\frac{1}{2}$, soit par l'acool à 90° pendant 3 minutes —lavage.

Dès les premiers jours c'est à dire après 4 ou 8 jours, des différences se manifestèrent dans la coloration et dans la forme du bacillus tuberculeux maintenu en solution glycogénique. La coloration était très imparfaite, très incomplète, si au niveau des agglomerats microscopiques les plus volumineux plus particulièrement dans leur partie superficielle des bacilles tuberculeux paraissent suffisamment bien colorés, un grand nombre de bacilles des parties profondes, comme les bacilles des petits agglomerats ou les bacilles isolés étaient fort mal colorés ou non colorés, représentant de petites masses refringentes ou de petits bâtonnets refringents, difficiles à percevoir. La plupart des bacilles colorés étaient granuleux.

Les preparations du bacille tuberculeux conservé dans l'eau distillée sterilisée permettèrent de constater également de petits amas ou des bacilles tuberculeux isolés, mal colorés ou non colorés, mais les bacilles pour le plus grand nombre étaient bien colorés à peine granuleux. Ces preparations à première une paraissaient riches de bacilles alors que les précédentes parais-

saient pauvres, si l'on ne prenau soin de référer tous les bacilles non-colorés. Les résultats nous ont paru similaires, au début, pour les solutions de 0.20 centig. ou de 0.40 centig. de glycogène; mais à une période plus avancée la solution la plus riche en glycogène nous a semblé exercer une action plus marquée. Par contre les différences de température n'ont en aucune influence. Dans les preparations faites après trois semaines, 1 mois et plus de séjour, les altérations du bacille tuberculeux maintenu dans les solutions glycogéniques furent de plus en plus marquées. Le nombre des bacilles non colorés fut de plus en plus grand, la forme de ceux qui étaient irrégulièrement colorés était très modifiée, très amincie, très grêle, ils étaient souvent à ce point granuleux, vacuolisés que certains agglomerats paraissaient des zooglées de microbiques.

Sans vouloir insister plus longtemps sur les résultats d'expériences que nous poursuivies encore, nous voulons simplement conclure.

1. Que le bacille tuberculeux humain, incorporé dans les conditions expérimentales exposées à des solutions de glycogène subit des modifications réelles de forme et une diminution marquée de l'acido-résistance comparable en quelque mesure à celles observées par MM. Arloing et Courmont dans leurs cultures homogènes.

2. Que cette double action "in vitro" du glycogène permet de lui accorder un rôle dans les processus complexes que rendent la coloration du bacille tuberculeux ou sa recherche au niveau des lésions tuberculeuses hépatiques si aléatoires.

INJECTIONS D'AZOTE ET LÉSIONS TUBERCULEUSES DES SÉREUSES.

Par Dr. Pierre Teissier,
Paris.

Depuis la communication du Professor Potain en 1888 sur le traitement du pneumothorax par les injections d'air sterilisé le procedé des injections gazeuses est entrée dans la thérapeutique des lésions tuberculeuses des séreuses. J'ai pour ma part, à la suite d'expériences, dont les résultats ont été communiqués au Congrès de la tuberculose en 1898, acquis la conviction que les injections gazeuses dans les séreuses ont une utilité incontestable pour les formes de tuberculose pleurale avec épanchement, et aussi pour les péritonites tuberculeuses avec ascites. J'ai notamment dit à ce moment pourquoi dans l'ascite tuberculeuse, l'injection devait être preférée à la laparotomie. Sans vouloir revenir ici sur les faits cliniques et expérimentaux que m'ont permis à cette époque de préconiser cette intervention dans la peritonite, je voudrais, la discussion subsistant encore sur le point de savoir s'il convient d'utiliser l'air, l'oxygène, ou l'azote, rappeler des recherches que j'ai poursuivies in 1897, 1898, relativement à l'influence curative et préventive de l'air, de l'oxygène, de l'azote de l'acide carbonique injectés dans le peritoine d'animaux préalablement ou ultérieurement tuberculisés au niveau de cette séreuse. Ces recherches m'ont permis d'affirmer la supériorité de l'azote pour les raisons suivantes que jerésumerai simplement ici.

1. Pour empêcher dans les épanchements tuberculeux après évacuation du liquide, sa réproduction, pour maintenir notamment au niveau du poumon tuberculeux la compression élastique dont l'influence est si heureuse, ou pour empêcher de façon prolongée la contact des feuillets pleuraux ou peritoneaux, et aussi s'opposer à la greffe des lésions tuberculeuses il importe avant tout de s'addresser à un gaz qui se resorbe lentement. Or, les observations de Demarquay, les recherches de Potain, celles qu'il a poursuivis avec Drouin et moi-même comme celles de Rodet et Nicolas, demontrent que l'azote est de tous les gaz utilisables de cette façon celui que se resorbe le moins vite. Lorsqu'on recueille, après un temps variable, l'air qui a été injecté dans une cavité séreuse (plèvre, peritoine) on s'aperçoit que la composition est modifiée, que l'azote demeure alors que le oxygène a notablement diminué. De telle sorte qu'injecter de l'air dans une séreuse, revient,

indirectement, a injecter de l'azote. J'ai pour ma part pu constater la persistance d'assez fortes proportions d'azote, injecté plusieur semaines avant à la dose de 400 cc. dans le peritoine de lapin, de 150 cc. dans le peritoine de cobaye.

2. L'azote est un gaz inerte, qui ne provoque aucune irritations au niveau des lésions. Demarquay a constaté (1859) que le maintien d'une atmosphère d'azote autours des places exercait une action sédative de la douleur et provoquait une excitation beaucoup moindre que carbon dioxid et h.

3. Si enfin comme je l'ai fait, on ensemence comparativement sur de larges surfaces de bouillon ou gélose glycériné, disposés en flacon de Ternbach, du bacillus tuberculeux et si on maintient ces cultures dans une atmosphère d'oxygène d'azote ou simplement d'air, on observe que les cultures soumises à l'influence de l'azote, se développent difficilement, forment un voile transparent, mince, où l'on ne découvre que des bacilles courts, grêles, nettement vacuolisés ou granuleux, du genre de ceux que l'on constate dans les cultures vieilles.

Ces faits légitiment, me semble-t-il, suffisamment l'usage des injections d'azote de préférence aux injections d'air et surtout aux injections d'oxygène, dans le traitement des formes de tuberculose des séreuses avec épanchement. Il reste, bien entendu, que dans les cas ou l'où n'aurait point à sa disposition de l'azote pur, l'emploi de l'air stérilisé garde toute la valeur que les travaux de Potain ont determinés.

SECTION I.

Pathology and Bacteriology (*Continued*).

FIFTH DAY. MORNING SESSION.

Friday, October 2, 1908.

PATHOLOGICAL ANATOMY AND HISTOLOGY.

The Section was called to order by the President, Dr. William H. Welch, at half-past nine o'clock.

THE TISSUE LESIONS PRODUCED BY THE TUBERCLE BACILLUS.

By William T. Councilman, M.D.,
Boston.

Our knowledge of the tuberculous lesions has greatly extended in the years which have elapsed since the discovery of the tubercle bacillus. The certainty of diagnosis which the presence of the organism gives does away with the former uncertainty, and we undoubtedly now recognize certain lesions as tuberculous which formerly were not so considered. With the greater opportunity for experimental work we are enabled to study the beginnings of processes, and by varying the conditions of the experiment, to produce equally numerous variations in the lesions. Every one who has worked with the disease, whether in man or animals, is conscious of the many forms of the lesions. While it may be safely said that no organism produces constantly histological changes so characteristic as to give certainty of diagnosis, this is particularly true of the tubercle bacillus. There is no form of degeneration, no tissue change accompanying other infectious diseases, which may not be encountered in tuberculosis. While this is true, there is yet a certain specificity in the process, shown by the character

of the primary tissue injury, the degenerations, the tissue reactions, and the sequences of these, which enable us, in the majority of cases, to make a diagnosis without recourse to bacteriological methods. What is true of tuberculosis is true, but to a lesser degree, of the action of other micro-örganisms. The acute lesions produced by the more typical pyogenic organisms have a character and a sequence which is almost invariably repeated, yet the more chronic lesions show very different cellular changes. This is still more the case with those organisms whose action is essentially chronic, as the leprosy bacilli. The histological pictures presented by the cutaneous lesions, the lymph-nodes, and the nervous system have but little in common.

When we consider the number of factors which enter into a tuberculous infection it is easy to see why the anatomical lesions should so differ. Many of these factors we know, and it is probable that there are others of which we are ignorant. Our knowledge of the disease, derived from experimental and comparative methods, has enabled us to comprehend certain lesions as due to the interaction of a number of factors. We are still ignorant of the conditions under which certain lesions, namely, those characterized by extensive exudations, arise. The character of a tuberculous lesion may be modified by—

(1) *The Character of Bacilli.*—That the tubercle bacilli may be divided into certain well-recognized varieties which, with slight and uncertain morphological and cultural differences, yet differ in their parasitic action, and that within these varieties there are individual strains with slighter differences, is now generally recognized. These differences in the bacilli are best brought out by experiments on the less susceptible animals. We speak of the greater or less degree of virulence of the bacilli, and it is probable that under virulence we must include both capacity for parasitic growth and toxin production. We may find in the lesions enormous numbers of bacilli with little evidence of toxin action or the reverse.

(2) *The Number of Bacilli.*—This is especially striking in animal experimentation. A variety of lesions may be so produced, and animals ordinarily not susceptible to a certain culture may be infected by a large dose. How much this factor of quantity enters into infection under natural conditions and in man we do not know, but it is safe to say that it is of importance.

(3) *The Character of the Tissue.*—This is shown best by the relative degrees of susceptibility of the different animal species and the character of the tissue changes in each. Susceptibility influences the character of the anatomical lesion in the variations which it produces on the relations of the processes of degeneration and destruction, compared with those of repair. Man must be considered among the more susceptible animals.

Not only does his social life expose him to opportunities for infection, but also the general and local defenses are weak. Within the animal species there are individual differences which can be transmitted by heredity. The weight of evidence seems to be strong that the disease in the ascendants leads to an increased susceptibility in the descendants. Susceptibility must depend upon the characters of the tissue fluids and cells, and the recent studies of the blood-cells and serum have shown that, within the species, there are marked individual differences. There is also a varying degree of susceptibility of organs. When the tubercle bacilli find access to the blood, and by means of this are distributed everywhere, in certain of the organs we never find lesions produced by them, in others only occasionally, in others the lesions are numerous, but their character shows that the tissue defenses have quickly overcome the attack. In other organs again the lesions are numerous and pursue their course unchecked. There may be local susceptibility in tissues, due to the persistence of the results of previous injury, and which acts mainly by local interference with the circulation. The evidence of the effect of trauma in the production of bone tuberculosis is too strong not to be taken into account. Defective nutrition, whether local or general, increases susceptibility. Age has a marked influence on the character of the lesions in both animals and man. The solitary tubercles of the brain and the large tuberculous lesions around the bile-ducts are chiefly found in children. Acute miliary tuberculosis of the lungs presents a different anatomical picture in children as compared with adults—exudation enters more largely into the formation of the tubercle in the child. The character and extent of lesions are also influenced by the anatomical structure of an organ. Organs provided with open canals or passages by means of which the products of disease may be easily distributed throughout the organ give numerous and varied lesions.

(4) *Mode of Entrance of Bacilli in the Production of the Primary Lesion and Their Secondary Distribution in the Body.*—There is at present a great deal of contention as to the most common mode of primary entrance, whether it be by the respiratory or digestive mucous membranes. Infection certainly takes place both from these surfaces, from the genito-urinary surfaces, and from the skin. The bacilli may be carried from the primary focus by the movement of the tissue fluids, by means of ameboid cells, by the lymphatics, and by the blood-vessels. The distribution may be continuous or at intervals; there may be a slow distribution of single bacilli or a sudden flooding of the tissues with great numbers.

(5) *The Influence of Mixed Infections.*—These may affect the lesions both by a general change in the cells and tissue fluids and by the production of local lesions. The pyogenic bacteria stand in the most intimate relations

with the tubercle bacilli, especially in such animals as man, in whom the chronic lesions lead to ulceration.

The tuberculous lesions are due to the interaction of exudations, tissue formation, and degeneration, and so are the lesions of any infectious disease. But, generally speaking, there are in tuberculosis special distinguishing characteristics in all three processes. More generally than in any other infection do the lesions occur in minute miliary foci. These foci, the miliary tubercles, form the leading characteristic of the disease. Certain cellular elements in certain combinations almost invariably are found in them. The most prominent cells, which are generally distinguished under the name epithelioid, from a vague similarity to epithelium, have an oval, round, or irregular nucleus, which is vesicular and contains but little chromatin. The cytoplasm is pale, non-granular, often irregularly vacuolated, and the cell outlines indistinguishable, being more or less in contact. Often forming the center of such an area or at one side there is a giant-cell with many nuclei. The nuclei of these are usually arranged around the cell, with their long axes pointing to the center. In some cases they are arranged at either end of an elongated cell, and in rare instances they are irregularly distributed. Between the epithelioid cells in some cases there is the appearance of a reticulum in which the cells lie. We may find the tubercles represented by such structures as described, but in most cases other cells are found. Polynuclear leukocytes may be found between the cells in all parts of the nodule, and in the periphery varying numbers of cells belonging to the lymphoid series. With appropriate stains fat-droplets, often in considerable amount, are found within the cells. The center of the nodule soon undergoes a peculiar degeneration. The cells lose their outlines, the nuclei no longer stain, and the whole is converted into a homogeneous mass in which stainable points of nuclear detritus may be found. This, the caseous degeneration, is a form of coagulation necrosis, and is due to changes in both the cells and the fluids around them. This material exerts a positive chemotaxis for the polynuclear leukocytes, and the more pronounced it is, the more numerous are they. There is now a more general agreement as to the genesis of the cells which form the tubercle than was formerly the case, although there is confusion arising from different views as to the nature of the cells from which the tubercle is formed, but especially from the nomenclature, which is peculiar to each investigator. The epithelioid cells of the tubercle do not arise from the fixed cells of the tissue except in certain places. They arise from the endothelial cells. Under this name I mean cells which are formed from the endothelial cells of blood-vessels and sinuses, from lymph-vessels and lymph-sinuses. They form a definite proportion of the leukocytes of the blood, a large part of the wandering cells of the tissue. They are ameboid, and their chief source at any given point is by migration from

the blood-vessels, although they may be added to by proliferation of the local endothelial cells. The experimental study of the disease has shown that, preceding the presence of these cells, small masses of bacilli in the tissues may be surrounded and engulfed by polynuclear leukocytes. These, however, are rapidly destroyed, and bodily or in fragments are taken up by the endothelial cells. The giant-cells represent a form of syncytium due to the fusion of the endothelial cells. The only fixed cells of the tissue which take part in the formation of the tubercle are the epithelial cells of the pulmonary alveoli and the lining epithelium of serous cavities. The cells of the tubercle form no intercellular substance. What appears as a reticulum is partly the adherent processes of the epithelioid cells, the old intercellular substances separated by the cells or coagulation products. The miliary tubercle does not tend to progressive enlargement. As the tubercle is forming a reactive inflammation is set up around it, the newly formed tissue has a relative degree of immunity to the action of the bacilli, and the tubercle enlarges by the bacilli being carried outside of the immune zone and the formation of new tubercles around it. Most tubercles visible to the naked eye are not single, but conglomerate. The tubercle enlarges not by expansion, but by dissemination of the bacilli and the formation of new nodules around the old. With the advance of the caseation the single centers of this coalesce into a large central area. The large solitary tubercles of the brain and the large tubercles of the internal organs are usually formed in this way, and the single centers can be recognized. The bacilli are present in the miliary tubercles in variable numbers, this depending to some extent upon the organ investigated,—in the liver, for example, very few are found. They are in part within the epithelioid and giant-cells, in part between them. They are rarely found within polynuclear leukocytes, and never within the lymphoid cells. Their dissemination into the surrounding tissue is due to the streaming of the tissue fluids. In our study of the more solid elements, the cells and fibrils, we are too prone to lose sight of the fact that they lie within a fluid. The extent of the reactive inflammation in the tissue immediately around the nodule varies both in animal species, in individuals, and in organs. It may be abundant or it may be absent, and the degree of its formation is an index of the resistance of the tissue to the influence of the bacilli and their products. There are no vessels in the tubercle. Occlusion of vessels takes place both by thrombosis and by the proliferation of their endothelial cells, which may take part in the formation of the tubercle. Exudation to a varying degree takes place, fibrin is often present between the cells of the tubercle itself, and the entire nodule may be surrounded by an exudation. I have devoted this much space to a description of the miliary tubercle because it is the type of the process, and in it may be found in varying degree all the anatomical pathological

processes concerned in the disease. While constantly present, these small nodules form, except in acute miliary tuberculosis, but a small part of the lesions of the disease.

Closely allied to the miliary tubercle is the diffuse formation of tuberculous tissue. In this there is the same tissue formation of epithelioid and giant-cells, with a varying degree of exudation and tissue reaction. There is not a formation of distinct nodules, but the tissue extends without sharp limitation, and the caseation occurs in irregular areas. We find this formation in relatively resistant tissue, as in the fibrous tissue around joints and in the newly formed tissue around old tuberculous cavities in the lung. The bacilli are always in small numbers and are contained within the cells.

The processes in which exudation is chiefly or only concerned play the greatest rôle in tuberculosis. The grave lesions of the disease are due to the softening and breaking down of such exudations. The exudations may be purulent, fibrinous, or serous; with every combination of these. The exudation usually persists, the cells in it undergo the same coagulation necrosis as the cells of the tubercle, the fibrin becomes swollen and hyaline, and the fluid, by condensation and coagulation, converted into thick gelatinous material. In the lungs particularly and in the meninges exudation plays an enormous part in the process. The tubercle bacilli may act as distinct pyogenic organisms. I have found distinct purulent foci in the lungs, with central softening and with no more reaction in the surrounding tissue than would be found in an abscess. It is not very uncommon to find purulent meningitis without distinct tubercles or tuberculous tissue. Caseation of the exudation takes place if it persists sufficiently long. In these cases I have usually found great numbers of tubercle bacilli, often closely packing the polynuclear leukocytes. Such cases have run an acute course, and depend either upon organisms with great power of growth and feeble toxic action, or upon peculiar conditions in the infected individual. The lack of toxin formation may be argued from the presence of the bacilli in intact leukocytes, and from the absence of tissue necrosis. The exudation may occur in miliary form. In one case of acute miliary tuberculosis in a child, which ran a very acute course, the tissues were sown with incredible numbers of small foci composed chiefly of bacilli masses and fibrin, with but few leukocytes and absence of tissue reaction, save the occasional presence of a giant-cell. In this case there was the most extensive formation of bacilli I have ever seen. They were found in the blood, both free and inclosed in cells, and the endothelial cells of the liver sinusoids contained them in large numbers.

Tuberculous pneumonia is such a vast subject that it comes outside of such a vague general discussion of the subject as this. It occurs in all of the anatomical forms of pneumonia; like these, it may take an acute or

chronic course. Too much emphasis cannot be laid on the importance of the rôle it plays in the disease. I do not, however, feel that we possess at present an adequate explanation of it. The same thing is true of ordinary lobar pneumonia. Our knowledge of infectious processes as they occur elsewhere in the body fails to explain all the facts of this disease.

The general and remote effects produced by the tubercles, apart from their presence and due to toxic absorption, have nothing specific in their character, and are not so marked as in some of the other infectious diseases. They consist of various degrees of degenerative lesions, not falling with special severity on any single organ, unless possibly on the kidney. It is, of course, impossible to separate lesions due to absorption of bacterial toxins from those due to the other incidents of the disease, as from the products of the accompanying mixed infections, the products of tissue necrosis, etc. Such lesions, in my experience, occur with greater frequency in man than in the experimental disease in animals.

DES CARACTÈRES ANATOMIQUES DE L'INFECTION TUBERCULEUSE. RAPPORTS AVEC LA RÉACTION A LA TUBERCULINE.

PAR S. ARLOING,

Lyon.

L'infection tuberculeuse se manifeste-t-elle toujours par quelque lésion macroscopique plus ou moins evidente? Le travail que nous présentons a pour but d'attirer tout particulièrement l'attention sur cette question.

Pour confirmer post-mortem l'existence d'une infection tuberculeuse admise ou soupçonnée pendant la vie du sujet, on a l'habitude de chercher une lésion perceptible au toucher et à l'oeil. Il peut arriver que cette lésion soit très-minime et sa recherche très-laborieuse. Lorsqu'on l'a trouvée, l'infection tuberculeuse est confirmée. Si la recherche est sans résultat, l'existence de la tuberculose est niée ou fortement mise en doute.

D'ordinaire on ne procède pas a l'examen histologique des organes d'élection. L'intervention du microscope est limitée a l'étude de la ou des lésions macroscopiques que l'on a rencontrées, s'il subsiste un doute sur leur véritable nature.

Des l'année 1901, dans mon travail sur l'Unité de la Tuberculose inséré au Bulletin de l'Académie de Médecine de Paris, puis en 1902, dans une Communication faite devant la Commission internationale de la Tuberculose, à Berlin; enfin, en 1903, dans un Rapport presenté au Congres international d'Hygiène et de Démographie, à Bruxelles, j'ai insisté pour faire admettre que l'infection tuberculeuse expérimentale peut se borner a produire des lésions très-minimes, insoupçonnées a l'oeuil nu, qui veulent être cherchées par les méthodes histologiques. Je prévoyais même des cas ou l'infection n'aurait pas déterminé ou ne déterminerait peut-être jamais de lésions très-claires.

J'ai d'abord signalé l'obligation de recourir à des examens histologiques, en présence de la facilité avec laquelle on décidait de l'echée ou du succes des inoculations faites dans le but de separer catégoriquement le bacille de la tuberculose humaine de celui de la tuberculose bovine.

Je disais, dans mon Rapport de Bruxelles, qu'il était dangereux, lorsqu'on

cherche les résultats d'une inoculation, de se borner à un examen macroscopique; car il m'était arrivé, a la suite d'une injection intra-veineuse de certains bacilles peu virulents pour le boeuf, d'apercevoir sur des coupes histologiques du poumon de très-fins tubercules accolés aux bronches ou bien intra-alvéolaires, alors que l'exploration soigneuse du poumon au toucher et a l'oeuil nu avait comporté un diagnostic négatif. Je faisais la même remarque pour des lésions extrèmement minimes des ganglions lymphatiques, du foie, des reins et de la rate que l'oeuil seul est impuissant a révéler.

Conséquemment, ajoutai-je en terminant, l'appreciation rigoureuse des résultats demande l'intervention des examens histologiques. Je sais bien que l'infection latente du système lymphatique par le bacille de Koch a été décélée par l'inoculation de la pulpe des ganglions au cobaye, et que, par ce procédé, on a demontré la présence de l'agent virulent dans des ganglions de l'homme en apparence sains. Semblable observation a été faite sur la mamelle de la vache. J'ai fait moi-même plusieurs constatations du même genre sur des ganglions d'aspect normal prelevée sur des boeufs tuberculeux, loins du siège des lésions. De plus, à la suite d'inoculations soucutanées pratiquées sur des animaux de l'espèce bovine, avec des bacilles humains, j'ai montré l'existence des bacilles dans des ganglions lymphatiques correspondants exempts de lésions tuberculeuses macroscopiques, en inserant la pulpe de ces ganglions dans les veines du bouvillon ou dans le tissu conjonctif sous-cutané du cobaye.

Mais l'inoculation, prouvée comme la méthode de choix pour révéler l'infection tuberculeuse latente, peut être inoperante si les organes hebergent des bacilles incapables de forcer la résistance offerte par le sujet révélateur, soit à cause de leur rareté, soit à raison de l'affaiblissement de leur virulence.

Pour compter sur l'inoculation, il faudrait la pratiquer sur plusieurs espèces animales douées de réceptivite differente, et, sur chaque espèce, par plusieurs voies.

L'histologie me parait donc appelée à jouer un rôle très-important dans la recherche des infections tuberculeuses; l'inoculation doit intervenir conjointement; l'une ou l'autre des techniques, ou l'une et l'autre, nous fournirait les indications souhaitées.

Ces preliminaires doivent bien faire saisir l'objet du présent travail et le caractère par le quel il se distingue des recherches poursuivies deja sur les tuberculoses latentes ou mieux sur les tuberculoses dissimulées.

* * * *

A part les cas ou les bacilles, inoculés depuis peu de temps, se disséminent en quelque sorte dans l'organisme et n'ont pu provoquer encore la réaction anatomique caractéristique (1), l'infection tuberculeuse dissimulée ou latente coexiste avec des bacilles d'une virulence attenuée, et non avec des bacilles

d'une virulence forte ou moyenne. Comme je soutiens depuis 1883 la variabilité du bacille de Koch, et comme je me suis attaché, dans ces diz dernières années, à montrer l'existence de variétés affaiblies, sur l'homme et les animaux contractant couramment la tuberculose, et même a créer artificiellent des variétés, j'ai été amené à etudier avec beaucoup de soins l'infection par des bacilles très-inégalement virulents.

En me livrant systematiquement a l'examen histologique d'un nombre considerable de pièces provenant d'un grand nombre de sujets d'espèces diverses infectés avec des bacilles variés, j'ai acquis la conviction que beaucoup de médecins ou d'experimentateurs non specialisés ont besoin de rectifier leurs idées sur les caractères de l'infection tuberculeuse. On croit, en effet, trop facilement que l'infection bacillaire doit se traduire au moins par quelques granulations, une seule peut-être, dans un récoin plus ou moins caché de l'organisme.

Le lecteur qui aurait cette idée l'abandonnera peut-être après avoir pris connaissance des observations que je vais résumer sur les suites des inoculations intra-veineuses prises comme type.

Je n'irai pas plus loin sans dire tout ce que je dois au concours de M. Paviot, professeur a la Faculté de Médecine, et de M. le docteur Lucien Chevenet, mon assistant.

I. Les bacilles humains, cultivés sur milieux solides, d'une virulence forte ou moyenne, injectés dans les veines des jeunes ruminants et du lapin, engendrent des lésions macroscopiques du type Villemin dans les poumons et souvent aussi dans la rate et le foie, rarement dans les reins.

Je n'entreprendrai pas de décrire ces lésions, puisqu'elles ont des caractères histologiques connus de tous. Cependant, il est des cas particulièrement observés sur le boeuf (Arloing et Paviot), où des lésions pulmonaires ne renferment pas les cellules epithélioïdes, les cellules géantes ou les cellules embryonnaires, eléments classiques du tubercule, mais revetent l'apparence d'une pneumonie catarrhale ou de blocs cellulaires intra-alvéolaires de caséification en masse, ou ont encore, dans certains organes, autres que les poumons, une structure plus ou moins fibreuse.

Si la virulence des bacilles est au-dessous de la moyenne, les lésions peuvent échapper a l'examen superficiel des viscères et au palper. On croirait a l'echée de l'inoculation. Mais si l'on fait des coupes microscopiques a travers les organes précités, l'examen permettra de voir des granulations du type Villemin, dans la plupart d'entre eux. Toutefois, ainsi que je l'ai fait remarquer avec Paviot, les lésions sont moins bien caractérisées dans le poumon que dans les autres organes. Par example, on rencontre dans le poumon des formations exclusivement embryonnaires ou des formations nodulaires dont le centre commence a devenir granuleux. L'incerti tude que l'on éprouve en leur présence se dissipe par la découverte d'une

cellule géante dans une des lésions pulmonaires ou dans les lésions beaucoup mieux caractérisees siègeant ailleurs. Aussi est-il nécessaire d'étendre l'examen histologique au foie, aux ganglions et a la rate. Dans les lésions de ces organes, notamment dans celles du foie et des ganglions, on trouvera l'elément ou la disposition qui renseignera sur la nature de la lésion pulmonaire.

II. Si on étudie l'infection produite par les variétés de bacilles attenuées, il sera donné d'observer des altérations encore plus intéressantes.

a. Que l'on injecte, par exemple, dans les veines du lapin $\frac{1}{4}$ à $\frac{1}{2}$ c.c. du bacille humain que j'ai modifié par la culture dans les profondeurs du bouillon glyceriné, on produira avec ce bacille les lésions du type Yersin attribuées par les auteurs a l'infection intra-veineuse du lapin par le bacille aviaire.

A l'oeuil nu, le poumon, le foie paraitront normaux; la rate sera souvent hypertrophiée, parfois elle conservera son volume habituel. On n'apercevra pas de granulations comme dans le type Villemin.

Malgre les apparences, le foie est plus ou moins alteré par des infiltrations de cellules rondes qui, procédant tantot des espaces de Vrieman, tantot du pourtour de la veine sus-hépatique, disloquent, isolent les cellules hépatiques et remplissent des sortes de logettes creusées dans le tissu du foie. Souvent l'infiltration se montre ça et la en plein lobule. Sous l'influence des variétés de bacilles les plus affaiblies les lésions hépatiques ne renferment pas de cellules géantes. Celles-ci se montrent, au contraire, sous l'influence des variétés les moins attenuées.

Les cellules géantes se developpent souvent dans la rate, a l'interieur ou en dehors, des follicles de Malpighi, accompagnées ou non d'elements epithélioïdes dans lesquels sont inclus des debris de cellules rouges. La aussi, les cellules géantes peuvent manquer, et la lésion consiste en cellules epithélioïdes plus ou moins nombreuses et plus ou moins visibles. Le foie et la rate sont les deux organes le plus gravement atteints. Quant au poumon, il est indemne ou à peine touché. Ses lésions, toujours micro. scopiques, consistent en tubercules atypiques dont la nature est dénoncée par leur étiologie et par leur coexistence avec les lésions hépatiques.

Le rein présente aussi ca et la des infiltrations de petites cellules nuclées dans la substance corticale et aussi du tissu conjonctif hyperplasie qui penetre dans la substance médullaire en suivant les tubes ansiformes.

Quand les bacilles en question s'introduisent en grand nombre dans les ganglions lymphatiques, ils determinent le gonflement de ces organes, sorte de lymphite temporaire, ne tardant pas a se dissiper. Lorsque le gonflement a disparudans beaucoup de ganglions l'examen histologique est négatif- Cependant, une étude plus approfondie pourra faire découvrir, dans certains ganglions, des points où les cellules a protoplasme trouble et granuleux ont de la tendance a se fusionner avec les cellules voisines.

b. Si l'injection introduit une très-faible quantité de bacilles ($\frac{1}{1000}$, $\frac{1}{5000}$, de centimètre cube) non seulement les viscères, examinés au bout de 2 à 3 mois, paraissent intacts, mais encore les altérations microscopiques y sont extrêmement réduites. À peine si l'on voit, sur les coupes du foie, de rares points infiltrés de cellules mêlées. L'infiltration est quelquefois tellement réduite que l'on éprouve les plus grandes difficultés à dire si elle est pathologique ou normale. De même, dans la rate, on a de la peine à trouver des cellules d'apparence épithélioïde ou des cellules à protoplasme granuleux tendant à se fondre avec les voisins. Cependant les lapins qui ont reçu ces faibles doses ont bien été sous le coup d'une infection tuberculeuse, car celle-là deviendra manifeste sur quelques individus. Effectivement, les lapins qui survivent longtemps présentent fréquemment des arthrites ou des synovites spécifiques, les viscères conservant leur intégrité anatomique.

III. Supposons maintenant que $\frac{1}{2}$ c.c. de culture de bacilles humains ou bovins en bouillon (culture homogène), dose forte pour le lapin, soit injecté sur des sujets de l'espèce bovine, il deviendra à peu près impossible de déceler des lésions histologiques dans le foie et les autres viscères, à cause de leur rareté et de leur minime importance. Pourtant, ces animaux réagissent positivement à la tuberculine, appliquée sous la peau ou à la surface de la conjonctive et agglutinant le bacille de Koch à l'instar des tuberculeux Autrement dit, ils présentent tous les signes révélateurs de la tuberculose. Ces faits nous conduisent donc jusqu'à l'infection tuberculeuse septicémique véritable, laquelle échappe au diagnostic histologique pour tomber dans le domaine du diagnostic expérimental ou physiologique.

Je profite de l'occasion qui m'est offerte pour déclarer l'erreur que j'ai commise, au Congrès international de Médecine de Paris (1900), en donnant le nom de tuberculose septicémique à la maladie déterminée, *sur le lapin* par l'injection intra-veineuse de bacilles en culture homogène. À ce moment, je me contentai d'examiner la surface des viscères. Comme je n'avais pas relevé de lésions, je croyais à une septicémie ou bacillémie simple, d'autant mieux qu'à une certaine période de la maladie, j'avais constaté la présence des bacilles dans la rate et la moelle osseuse, par la culture. Nous savons maintenant que des lésions histologiques sont cachées sous une apparence extérieure normale, dans tous les cas où les bacilles sont injectés à dose notable. Mais les cas d'infection sans lésions décélables peuvent se présenter.

Il résulte des détails qui précèdent que l'existence de granulations agglomérées en plus ou moins grand nombre, palpable et visible à l'œil nu, aussi discrète qu'on peut les supposer, révèle non une tuberculose latente mais une tuberculose établie.

La véritable infection latente est réalisée par une invasion de bacilles qui n'a pas eu le temps de provoquer des édifications tuberculeuses ou qui disparait peut être sans déterminer de lésions.

Il résulte encore de ce travail:

1. Que l'infection tuberculeuse se traduit sur les mammifères ou avec des bacilles de mammifère, par des lésions microscopiques du type Villemin ou d'un type anormal qui sera dévoilé par l'examen histologique de tous les viscères où les altérations ont l'habitude de se développer.

2. Qu'elle se manifeste aussi par des lésions du type Yersin siégant dans le foie et la rate que rien ne laisse soupçonner à l'examen superficiel de l'organe. Ce sont les formes dissimulaires et non latentes.

3. Qu'elle se borne parfois produire dans la rate, les ganglions, l'apparition de cellules épithélioïdes ou de cellules géantes.

4. Que dans les cas 2 et 3, le poumon est généralement indemne.

5. Que souvent, dans ces formes dissimulées où cependant le microscope révèle des altérations histologiques, on voit se développer tardivement des localisations manifestes sur le système osséo-articulaires.

6. Qu'enfin, il faut presque renoncer à ne trouver la trace histologique lorsque l'infection est déterminée par un petit nombre de bacilles attenués sur des sujets de grande taille.

On objectera peut être que nous avons observé ces exemples de tuberculose dissimulée à la suite d'infections expérimentales avec des bacilles *ad hoc*, et que les conditions qui président à leur developpement n'existent peut être pas dans les contaminations naturelles.

Il est facile de répondre à cette objection. D'abord, il est dit plus haut que nous avons observé des cas de tuberculose dissimulée à la suite de l'inoculation de virus emprunté directement à des lésions tuberculeuses. Certains malades peuvent donc émettre des bacilles moins virulents qu'à l'ordinaire sur des sujets de la même espèce.

Ensuite, il est permi de prévoir qu'entre leur émission et leur pénétration dans de sujet contaminable, tels bacilles aurent pu subir des influences modificatrices qui lui rapprocherent plus ou moins de nos variétés expérimentales.

Et encore, que le hasard de contamination influence aussi sur la dose des agents infectieux. Enfin, la nature ne se charge-t-elle pas de nous préparer elle-même en tuberculose? Ne trouve-t-on pas sujets de l'espèce bovine ayant fort bien réagi à la tuberculine et sur lesquels un observateur prévenu ne rencontre pas la moindre lésion macroscopique?

Donc nos remarques doivent trouver à s'appliquer dans la pratique. Aussi disai-je quelques mots, en terminant, sur les rapports des caractères de l'infection tuberculeuse avec la valeur révélatrice de la tuberculine.

La tuberculine, comme agent révélateur, a été proclamé "défaillante"

lorsqu'elle ne dénonce pas une tuberculose existante ou lorsqu'elle dénonce une tuberculose qui parait matériellement inexistante.

Nous ignorons encore à l'heure actuelle le processus de la réaction tuberculineuse. Il serait donc téméraire de proclamer l'infallibilité ou de prétendre fournir une explication définitive défaillancer de la tuberculine. Cependant la pratique démontre que la tuberculine est un réactif révélateur très délicat et très précieux de la tuberculose.

Le nombre des erreurs qu'on lui impute diminuerent avec la scrupuleuse observation des règles qui doivent présider à son emploi et avec les soins que l'on mettra à rechercher des lésions tuberculeuses, parfois très limitées, à l'autopsie.

Il n'y a pas lieu d'attacher un gros intérêt avec cas où la tuberculose ne dénonce pas une tuberculose existante, car dans ces cas, les lésions sont très étendues, très amincies, les malades présentent ordinairement des signes cliniques. S'il s'agit de tuberculose bovine, le sacrifice d'un malade de cette sorte causera ni un sérieux dommage, ni une grande déception.

Mais, d'après ce qui est dit plus haut, on doit s'attendre:

1. À trouver des réactions positives coincidant avec des altérations anatomiques décelables seulement au microscope.

2. À ne pas pouvoir trouver méme au microscope la trace anatomique de la tuberculose.

Ces cas sont assurément rares. Ils rentrent parmi ceux où l'infection tuberculeuse est produite par une petite quantité de bacilles faibles ou par des bacilles introduits depuis peu de temps dans l'organisme et qui n'en pu encore y provoquer des lésions.

Voilà des idées à répandre dans le monde médical et parmi les éleveurs. Elles nous fait apparaitre la tuberculine comme un excellent révélateur de la tuberculose anatomiquement établie, aussi que de l'infection tuberculeuse sans lésions.

Anatomical Characteristics of Tuberculous Infections and Their Relation to Tuberculin Reactions.—(S. ARLOING.)

Does tuberculous infection always manifest itself by some more or less evident microscopical lesion?

The lesions which accompany tuberculous infection do not always present tubercles visible to the naked eye. Owing to the differences in the virulence of the bacillus, the lesions are sometimes extremely slight, and visible only in histological sections. Diminution in the virulence may bring about a certain modification, which in turn causes profound changes in the reactions of the organism. Not only must

the lesions be looked for with the microscope, but they no longer possess the classical histological characteristics. Finally, there are some cases in which the bacilli spread in the organism and exhaust themselves without leaving any trace of their passage. In such cases tuberculous infection shows itself only by the presence of bacilli in the tissues; or it may be revealed by experimental methods of diagnosis, especially tuberculin and the serum-agglutination test. Whatever may be the histological character of the tuberculous infection, the patient will at some time react positively to these experimental tests. Hence these tests reveal the existence of bacillary infection rather than the presence of appreciable tuberculous lesions. This being the case, it is to be expected that a disagreement, often more apparent than real, should be found between the experimental diagnosis and the post-mortem microscopical diagnosis.

The number of these discrepancies will be diminished by seeking out histological changes, and, if necessary, the bacilli themselves, at the autopsy. In the absence of both, a positive reaction to tuberculin should nevertheless be regarded as proof that a latent infection was either extending in the organism or in process of recovery.

During life the same significance should be attributed to a positive reaction, and in most cases the results will be found to be correct.

The above facts show the necessity of perfecting prognosis, as well as of methods of diagnosis, in order to foretell as accurately as possible the probable future of a tuberculous infection.

ÉTUDE ANATOMIQUE ET PATHOGÉNIQUE DES LÉSIONS NON FOLLICULAIRES DE LA TUBERCULOSE.

PAR LE DR. LÉON BERNARD,
Médecin des Hôpitaux de Paris.

Il est classique, depuis Laënnec, d'admettre que le tubercule est l'expression anatomique unique de la tuberculose, et d'exiger qu'une lésion contienne des tubercules pour la déclarer tuberculeuse.

A vrai dire, on sait que le nodule tuberculeux peut être provoqué par d'autres agents que le bacille de Koch. On reconnaît également que le tubercule bacilaire n'est pas toujours identique à lui-meme: le schéma classique du follicule, unité constituante du nodule tuberculeux, n'est pas toujours réalisé: la cellule-géante peut manquer; on décrit aussi des tubercules embryonnaires formés seulement de leucocytes agglomérés; enfin il existe des formations exclusivement épithélioïdes.

Toutes ces variétés sont comprises sous la même appellation de tubercules, ceux-ci étant considérés comme plus ou moins typiques.

Mais le domaine de la tuberculose s'est bien élargi dans ces dernières années: en France, principalement sous l'impulsion des découvertes et des idées de M. le Professeur Landouzy, un grand nombre d'affections ont été rattachées à la tuberculose, dont la véritable nature avait échappé à nos prédécesseurs en raison de leurs symptômes et de leurs lésions qui s'écartaient du cadre accepté des symptômes et des lésions de la tuberculose. On a pu longtemps discuter la légitimité de cette attribution; aujourd'hui la preuve est faite que le bacille de Koch peut déterminer des altérations n'ayant aucun des caractères du tubercule.

C'est l'étude de ces lésions que nous voudrions résumer ici négligeant les faits cliniques connexes de ceux que nous rapportons, et ne consignant que des faits anatomiques démontrés.

Le bacille de Koch est capable de provoquer dans les tissus des réactions identiques a celles que sollicitent les autres microbes; voilà la notion nouvelle que nous voulons établir sur ces exemples rigoureusement observés. Ces réactions diffèrent nécessairement suivant les tissus envahis.

Les tissus conjonctifs peuvent réagir au bacille de Koch selon diverses modalités. Dans le tissu conjonctif diffus, le virus tuberculeux, agissant soit d'une manière aiguë, soit d'une manière chronique, provoque soit l'infiltration lympho-conjonctive, soit la sclérose.

L'infiltration lympho-conjonctive (infiltration embryonnaire des anciens auteurs) d'origine bacillaire a été vue dans beaucoup d'organes; nous l'avons notée, dans le rein, et l'y avons reproduite expérimentalement par le bacille de Koch.

Gougerot a décelé le bacille dans des infiltrats lymphoïdes observés dans le foie, dans la langue et dans diverses lésions cutanées rangées sous le nom de tuberculides qui ont été reproduites pour la première fois expérimentalement par cet auteur.

Les scléroses bacillaires viscérales sont aujourd'hui bien connues: nous ne voulons pas parler ici de scléroses développées à partir et autour de tubercules fibreux; nous ne comprenons que des scléroses pures, dépourvues absolument de tubercules. Elles ont été rencontrées dans divers organes:

Dans le foie, les cirrhoses tuberculeuses sans tubercules, à forme hypertrophique ou atrophique, ne peuvent plus être contestées: découvertes par Hanot et Gilbert, leur nature véritable a été démontrée récemment; Triboulet (1903), Jousset (1903), Philibert et Blondin (1905), Gougerot (1908), ont prouvé, soit par la constatation directe du bacille soit par l'inoculation des lésions, que derrière l'alcoolisme se cache la tuberculose dans un grand nombre de cas de cirrhose hépatique. Expérimentalement, Hanot et Gilbert (1890 et 1892), Pilliet (1892) Haushalter (1893), Widal et Bezançon (1894), Claude (1903), Milian (1907), Gougerot (1908), ont pu obtenir des scléroses du foie avec le bacille de Koch.

Pour le rein, même démonstration: Jousset a décelé le bacille de Koch par l'inoculation dans la néphrite interstitielle (1904); nous-même, avec Salomon, avons, avec le bacille, provoqué chez le cobaye par inoculation intra péritonéale une néphrite interstitielle jeune.

Des scléroses bacillaires ont été encore mentionnées dans la rate par Jeanselme et Weil, chez l'homme, par Salomon et Pâris qui les réalisent chez l'animal;—dans les surrénales par Léon Bernard et Bigart;—dans la thyroïde par Roger et Garnier;—dans le pancréas par Carnot, qui les reproduit expérimentalement (1898).

Le tissu conjonctif séreux présente, au bacille de Koch, d'autres réactions: c'est en particulier l'exsudation serofibrineuse qui a été observée sur les diverses séreuses de l'économie; nous ne mentionnerons ici que les cas de serites sans tubercules.

On sait que, à la suite des travaux de Landouzy, la nature tuberculeuse de la pleurésie aiguë franche, dite autrefois a frigore a été définitivement acceptée; ces lésions s'accompagnent souvent de tubercules, mais non toujours: la lymphocytose de l'exsudat (Widal) autant que la présence du bacille sont les témoins de leur nature. Au niveau du péricarde, du péritoine, des méninges, des synoviales articulaires, des exsudats sero-fibrineux sans tubercules d'origine bacillaire peuvent également se développer. Siredey

et Tinel ont trouvé le bacille dans un exsudat méningé sans tubercules, Gougerot dans 3 cas analogues; Oddo et Olmer ont reconnu un cas de méningite spinale par l'inoculation; Renaud, Gougerot et J. Teissier ont provoqué avec le bacille des méningites expérimentales sans tubercules. L'inoculation positive de liquides articulaires a été obtenue par Dieulafoy et Griffon, Poncet et Dor, Milian, Delbet et Cartier, dans des cas d'arthrites d'allure rhumatismale, n'ayant aucun des caractères des tumeurs blanches.

La membrane interne du coeur et des vaisseaux est également susceptible de se recouvrir d'exsudat fibrineux sous l'action du bacille de Koch. Dans des endocardites secondaires, ayant évolué chez des tuberculeux, le bacille de Koch a été décelé par Lion (1892), Londe et Petit (1894), Leyden (1896), Etienne (1898), Cornil et Aguerre (1899), Ferrand et Rathery (1903), Lortat-Jacob et Sabareanu (1904), Oettinger et Braillon (1904), Barbier (1906); Braillon et Jousset ont même démontré la présence du bacille de Koch dans des cas d'endocardite primitive, à allure rhumatismale, à lésions purement fibrineuses (1903). Enfin, j'ai moi-même pu reproduire avec Salomon une semblable endocardite à végétations fibrineuses bacillifères par l'inoculation du bacille de Koch dans le coeur ou les artères de chiens ou de lapins sans traumatisme valvulaire (1905).

Nous avons obtenu de pareilles lésions pour l'aorte. Pour les veines, Lesné et Ravaut ont eu les mêmes résultats (1900).

Ces auteurs ont pu, après Chantemesse et Widal, Vaquez, Sabrazès et Mongour, déceler le bacille dans des phlébites thrombosantes chez des tuberculeux.

Le tissu adénoïde présente également, sous l'influence du bacille, des réactions banales, qui aboutissent à des lésions dépourvues de tubercules; c'est l'hyperplasie lymphoide simple, qui a été constatée dans les ganglions, (Berger et Bezançon, Sabrazès et Duclion), dans l'amygdale (Dieulafoy).

Les cellules nobles des parenchymes réagissent également au bacille; en particulier, les cellules épithéliales peuvent soit être frappées de dégénérescence, soit au contraire entrer en suractivité.

Toutes les variétés de dégénérescences cellulaires ont été rencontrées, dans les organes, au cours de la tuberculose; dans les glandes: tuméfaction trouble, dégénérescence graisseuse, nécrose de coagulation, dégénérescence pigmentaire des cellules; dans les organes de revêtement: dégénérescence muqueuse, dégénérescence cornée;—aux cellules nerveuses: dégénérescence colloïde et dégénérescence aqueuse vacuolaire;—aux vaisseaux: dégénérescence hyaline et amyloïde.

Les exemples de dégénérescences cellulaires, notées sur les organes de tuberculeux, ne se comptent plus.

Elles ont pu être reproduites expérimentalement pour la plupart: rappelons les expériences de Bouchard et Charrin, obtenant sur le lapin la dégén-

érescence amyloïde; celles de Péron, déterminant la stéatose du foie, confirmées par Gougerot; celles de Léon Bernard et Salomon, créant des néphrites tuberculeuses, avec dégénérescence des cellules tubulaires; corrélativement Jousset a décelé par l'inoculation le bacille dans des néphrites épithéliales.

Au contraire, les cas où une suractivite cellulaire localisée a pu être imputée à la tuberculose sont encore rares et d'interprétation discutable. On a cité des faits d'hépatite nodulaire et de transformation adénomateuse due à la tuberculose (Sabourin, Hanot et Gilbert, Chauffard); des adénomes ont été obtenus expérimentalement par Claude, puis par Gougerot.

L'irritation cellulaire, provoquée par le bacille peut aller plus loin et aboutir à des processus néoplasiques: parmi les tumeurs conjonctives rapportées au bacille de Koch, je citerai seulement un cas de fibrome de Landouzy et Laederich, et un lymphadenome cutané de Gougerot, où le bacille de Koch fut coloré. Le rôle de la tuberculose dans la genèse des tumeurs lymphomateuses est aujourd'hui partout accepté. On a également signalé des tumeurs épithéliales d'origine tuberculeuse (Ménétrier, Marfan, Claude, Danlos, etc.); mais le plus souvent le rôle du bacille est discutable, et il s'agit d'association de tubercule et de cancer, celui-ci se développant secondairement sur des tubercules.

Enfin, il est une forme de bacillose qui comporte, associées, plusieurs de ces lésions, c'est la typhobacillose, décrite en 1882 par Landouzy. On sait qu'à l'autopsie des sujets qui meurent dans la phase aiguë de cette maladie, on trouve la congestion des organes, des altérations dégénératives cellulaires, des infiltrats leucocytiques localisés principalement autour des capillaires, lésions semblables à celles des septicémies; elles sont ordinairement dépourvues de follicules; quelquefois seulement de rares granulations s'y surajoutent. La typhobacillose, comparable à la forme de bacillose expérimentale connue sous le nom de type Yersin, à été reproduite expérimentalement dans ses diverses variétés par Gougerot (1908).

Ainsi donc voilà bien des catégories de lésions n'ayant aucun rapport avec le tubercule, que peut provoquer le bacille de Koch: infiltrats embryonnaires et scléroses, exsudats fibrineux et dégénérescences cellulaires, hyperplasies et néoplasies, tous les processus histo-pathologiques, le bacille de Koch peut les réaliser, indépendamment de toute formation de follicule. Comme c'est là une notion nouvelle en phtisiologie, nous pensons qu'il y a intérêt à grouper tous ces processus dans une même famille; et nous avons proposé de les nommer d'un terme simplement anatomique, lesions non folliculaires, par opposition au follicule. Ces altérations ont parfois été désignées autrement, les mots "toxiniques" ou "inflammatoires" ont été employés: Le premier implique une notion pathogénique qui, nous allons le dire, s'est trouvée démentie par les faits. Le second (Poncet) a le tort de rejeter les lésions folliculaires du cadre général des processus inflammatoires,

ce qui est une erreur de doctrine. On s'est aussi servi du terme de lésion atypique, mais le mot atypique a été également employé pour désigner des formes cliniques de tuberculose; et il faut bien savoir qu'il n'y a pas nécessairement superposition entre l'atypie clinique et l'atypie anatomique; le mot "atypique" implique l'existence d'un type; or ce type apparaît variable suivant la conception régnante à ce sujet. Notre conception actuelle nous éloigne de l'idée d'un type unique, exclusif, mais bien plutôt elle nous conduit à considérer que la tuberculose est susceptible de déterminer des types lésionnels multiples, dont les uns ressortissent à la lésion folliculaire, les autres sont les lésions non folliculaires. La question qui se pose est de connaître le déterminisme de ces diverses lésions, et les rapports qui les unissent.

Nous serons brefs sur cette question de pathogénie, que nous avons développée ailleurs.* Pendant longtemps, les altérations que nous avons en vue furent considérées comme des complications de la tuberculose, et attribuées à des infections secondaires; cette doctrine n'est plus acceptée aujourd'hui; et le rôle de l'infection secondaire au cours de la tuberculose apparît singulièrement réduit d'après les derniers travaux.

L'opinion générale qui domine actuellement est que les lésions non folliculaires sont dues aux toxines tuberculeuses: on oppose le follicule tuberculeux, lésion d'origine bacillaire, aux lésions non folliculaires, d'origine toxique.

Aussi considère-t-on le premier comme spécifique, les secondes comme banales, semblables aux lésions toxiniques des autres infections. Nous pensons avoir montré dans différents travaux que cette conception repose sur des faits mal observés: les poisons diffusibles du bacille ou tuberculines étudiées expérimentalement, ne provoquent que des lésions minimes, inconstantes, nullement comparables aux lésions non folliculaires révélées par l'anatomie pathologique humaine. En outre la tuberculine des laboratoires ne peut être assimilée aux poisons naturels du bacille de Koch vivant dans l'économie (Arloing et Bancel); en vérité, l'expérimentation ne nous a rien appris sur l'intoxication tuberculeuse générale de l'organisme.

Au contraire, la plupart des lésions non folliculaires ont pu être reproduites avec le bacille de Koch, nous l'avons vu.

L'expérience a prouvé que le virus lui-même, par son action propre, est capable de déterminer toutes ces altérations d'infiltrations, de sclérose, d'exsudation, de dégénérescences cellulaires, sans aucune formation folliculaire. Aussi la tendance actuelle, depuis nos recherches et celles de Jousset, est-elle de considérer que le bacille de Koch lui-même commande la genèse de toutes les lésions de la tuberculose, aussi bien les lésions folliculaires que les lésions non folliculaires.

* Léon Bernard et Gougerot: "Pathogénie des lésions non folliculaires de la tuberculose," Bulletin Médical, 8 juillet, 1908.

Cette action, on sait aujourd'hui comment elle s'exerce: Auclair a démontré que le bacille contient dans son corps des substances toxiques (éthéro-bacilline et chloroformo-bacilline) qui ne se diffusent pas et localement provoquent la formation des tubercules; dans nos recherches avec Salomen sur le rein, nous avons vu que ces mêmes substances sont susceptibles de déterminer également des lésions non folliculaires. Donc toutes les lésions, causées par le bacille de Koch, sont sous la dependance de ses poisons locaux, et ces lésions impliquent la présence même du bacille là où elles existent.

Si le même déterminisme pathogénique commande toutes ces altérations, aussi bien n'y a-t-il pas de différence essentielle entre elles: on trouve les unes et les autres côte à côte sur un même organisme, sur un même organe; dans les expériences que nous avons faites avec Salomon sur les reins, nous avons vu que tous les intermédiaires s'observent entre les follicules les plus typiques, et l'infiltration embryonnaire diffuse la plus banale; sur un même rein, nous avons noté tous les faits de passage entre l'infiltration lympho-conjonctive en nappe et les nodules lymphocytiques, entre ceux-ci et les follicules caractéristiques; et nous y avons rencontré, voisine de ces lésions interstitielles, la dégénérescence des épithéliums tubulaires.

Comment alors reconnaître la limite entre les lésions non folliculaires et les autres, dont les types extrêmes paraissent si tranchés?

Ce qui caractérise le tubercule, c'est la caséification; celle-ci a son premier degré dans la dégénérescence vitreuse, qui atteint les cellules épithélioïdes. C'est donc en définitive la cellule épithélioïde, qui constitue la signature de toute formation folliculaire; les travaux les plus récents ont d'ailleurs démontré que, dans les parenchymes envahis par le bacille le processus épithélioïde frappe aussi bien les cellules nobles de ces parenchymes que les cellules lympho-conjonctives mobilisées.

Les processus lésionnels dûs au bacille de Koch, agissant par ses poisons locaux, peuvent se comprendre de la manière suivante, leurs variétés anatomiques répondant à des actions inégales du bacille: Au plus haut degré de puissance, les bacilles provoquent par leurs sécrétions toxiques la mort des tissues et une réaction leucocytaire diffuse: type de lésion non folliculaire, que l'on observe dans certaines altérations aiguës, massives, comme dans les méningites diffuses aiguës, dans les granulies, etc.

A un degré d'intensité moyenne, l'activité toxique des bacilles provoque une réaction de défense lympho-conjonctive et la dégénérescence spéciale qui se manifeste par l'épithélioïdisation, laquelle frappe les cellules nobles aussi bien que les cellules lympho-conjonctives de réaction; ainsi se forment, par l'agrégat de ces divers éléments, des follicules plus ou moins typiques. Enfin, à son degré le plus faible, l'action toxique spéciale du bacille est insuffisante à provoquer la dégénérescence vitreuse du processus épithélioïde; il provoque alors des réactions semblables à celles des autres microbes: infiltrations

lympho-conjonctive, nodulaire ou diffuse, qui peut se résorber ou s'organiser en tissu de sclérose; réaction fibrineuse des séreuses, etc.

Cette inégalité d'action du bacille ne semble guère explicable par une différence de virulence, ni par une qualité propre à celui-ci, puisque ces différentes lésions peuvent coexister côte à côte; la même raison paraît devoir réduire l'influence du terrain pour interpréter la différence des lésions.

Avec Gougerot, il nous a semblé que c'est le mode de disposition des bacilles dans les tissus envahis qui commande la nature de la lésion: pour une virulence donnée, ils déterminent tel ou tel des trois types généraux que nous venons de voir suivant qu'ils sont réunis en plus ou moins grand nombre. Nous avons constaté qu'ils sont agglomérés en gros amas dans les lésions dégénératives massives; en petits amas dans les follicules; qu'ils sont rares, épars, végétant à l'état d'unités isolées, dans les lésions simples de réaction interstitielle.

En résumé, les différentes lésions de la tuberculose représentent les diverses modalités réactionnelles des tissus au bacille de Koch, dont l'action s'exerce localement par les poisons spéciaux qu'il contient.

Les lésions non folliculaires et folliculaires forment une longue série ininterrompue de réactions subordonnées à l'intensité de cette action toxique: les réactions non folliculaires sont aux deux extrémités de cette série; les réactions folliculaires sont au milieu.

Mais aucune de ces lésions n'est spécifique: les follicules peuvent être provoqués par d'autres agents; les lésions non folliculaires sont celles de tous les microbes. Seule la cause des lésions est spécifique de la tuberculose, c'est le bacille de Koch.

DU PROCESSUS PNEUMONIQUE DANS LA TUBERCULOSE PULMONAIRE.

Par le Professeur Raymond Tripier,
de l'Université de Lyon.

Nous croyons avoir démontré que toutes les formations tuberculeuses dans les poumons, comme dans les autres organes, consistent dans un processus inflammatoire qui doit être considéré comme une exagération et une déviation des productions normales de l'organe affecté.* Nous avons aussi insisté sur ce fait que la nécrose caséuse, comme tout autre nécrose, procède toujours d'oblitérations vasculaires qui s'accompagnent forcément d'une augmentation compensatrice de vascularisation dans les parties périphériques dont les vaisseaux, restés perméables, sont en connexion avec ceux qui ont été oblitérés, et d'où résultent des scléroses susceptibles d'aboutir à la limitation et même à la cicatrisation des tubercules lorsqu'ils sont de petit volume. Mais dans le poumon devenu tuberculeux, on constate en outre des manifestations inflammatoires diverses, probablement encore sous l'influence des bacilles de Koch et de leurs toxines, et, suivant quelques auteurs, peut-être avec l'adjonction de l'action d'autres micro-organismes.

C'est d'abord un processus diffus sous la forme d'engouement d'intensité variable et surtout accusé au voisinage des lésions tuberculeuses, près des vaisseaux et des bronches. Ce sont aussi des productions broncho-pneumoniques et des noyaux de pneumonie lobulaire, parfois agglomérés au point de produire des amas psuedo-lobaires. Plus rarement il s'agit d'une pneumonie lobaire.

Lorsque ces lésions surviennent à la période ultime de la phtisie pulmonaire, elles entrainent ordinairement la mort du malade. Néaumoins ces productions pneumoniques ne se présentent jamais sous la forme d'une hépatisation grise, c'est toujours de l'hépatisation rouge que l'on observe avec plus ou moins d'engouement, seulement parfois avec des exsudats séreux exagérés, comme nous l'avons indiqué. Et c'est pourquoi lorsque ces lésions se produisant dans le cours de la tuberculose chronique, le plus souvent sous la forme lobulaire, elles se transforment en pneumonie hyperpla-

* R. Tripier: Congrès de Berlin, 1890, et traité d'anatomie pathologique générale, Paris, 1904.

sique sous l'aspect d'amas indurés, rougeâtres, ardoisés ou noirâtres, suivant leur ancienneté.

Nous avons décrit les lésions de pneumonie hyperplasique dans notre Traité d'anatomie pathologique, en insistant sur le fait de leur production à la suite d'une hépatisation rouge prolongée, c'est-à-dire avec persistance de la circulation sanguine dans les parties affectées, et même avec une augmentation de vascularisation sous l'influence d'un cœur plus ou moins hypertrophié. Or, dans la phtisie pulmonaire le cœur est souvent diminué de volume et de poids ou bien il est de poids à peu près normal, seulement avec une augmentation de volume du cœur droit, et les malades sont dans des conditions particulières de débilitation. Cependant c'est chez eux qu'on rencontre le plus fréquemment ces lésions de pneumonie hyperplasique; ce qui semble tout d'abord en contradiction avec les circonstances indiquées par nous comme favorables à leur production. Mais lorsqu'on veut bien se rendre compte dans quelles conditions la circulation s'accomplit dans les poumons affectés de tuberculose chronique, on arrive parfaitement à expliquer de la même manière la transformation hyperplasique des exsudats.

C'est que, sauf dans les points où il existe de la nécrose caséeuse, il y a partout une activité plus grande de la circulation. L'hépatisation rouge qui a pu se produire persiste avec peu de tendance à la résolution, en raison de la presistance des agents infectieux et d'un état fébrile. Il en résulte la continuation des phénomènes productifs jusqu'à l'édification de la pneumonie hyperplasique sur divers points, tandis que sur d'autres qui sont restés seulement engoués les éléments exsudés subissent la dégénérescence graisseuse.

Et si l'hépatisation grise ne se remarque jamais, c'est que précisément la circulation ne fait défaut qu'au niveau des points précédemment détruits, caséifiés ou en voie de caséification. Partout ailleurs la circulation est augmentée par compensation et d'autant plus que les productions tuberculeuses occupent une plus grande étendue depuis un temps plus long, avec la conservation d'une certaine énergie du cœur. C'est pourquoi les autres manifestations inflammatoires du poumon donnent lieu, soit à une sclérose diffuse lorsqu'elles sont légères et disséminées, soit à de la pneumonie hyperplasique lorsqu'elles sont localisées avec plus d'intensité à des groupes de lobules, jusqu'à la formation d'amas scléreux plus ou moins étendus, finissant par prendre l'aspect fibroïde intrathoracique. Et il s'agit on somme, pour touts les lésions pneumoniques aboutissant à une sclérose, des phénomènes de cicatrisation dont le mécanisme de production ressort des considérations précédentes.

The Pneumonic Process in Pulmonary Tuberculosis.—(TRIPIER.)

In the lungs the morbid process in every kind of tuberculous formation is pneumonic, and we observe the simultaneous tendency to diffuse

bronchopneumonic and lobular, sometimes pseudolobar, and exceptionally lobar inflammations, which, if the condition becomes chronic, result in hyperplastic and sclerotic changes.

If these productive phenomena, which necessitate an increase of the circulation, are frequently seen in pulmonary tuberculosis in spite of the debilitated state of the organism, it is because the caseous necrotic lesions which are produced by the obliteration of numerous blood-vessels are necessarily accompanied by compensatory vascular dilatation in other portions. Hence the diffuse pneumonic process is followed by diffuse sclerosis, and if hepatization takes place, it is never gray, but red, so that its persistence produces hyperplastic pneumonia and the fibroid changes which may be regarded as cicatricial.

El Proceso Neumónico en la Tuberculosis Pulmonar.—(TRIPIER.)

En los pulmones, el proceso mórbido en todos los casos de tuberculosis, es de carácter neumónico, y se observa una tendencia simultánea á una inflamación difundida de los bronquios y los lóbulos del pulmón, algunas veces esta es seudo-lobular y en casos excepcionales la inflamación es lobular; si la condición toma un curso crónico, esto da lugar a cambios hiperplásticos y escleróticos.

Si estos fenómenos productivos, que necesitan un aumento de circulación, son frecuentemente observados en la tuberculosis pulmonar, á pesar del estado debilitado del organismo, son debido al hecho de que las lesiones necróticas caseosas, producidas por la obliteración de numerosos vasos sanguíneos, van necesariamente acompañadas de una dilatación vascular en otra parte del cuerpo. Por lo tanto el proceso neumónico difundido es seguido de una esclerosis difundida, y si una hepatización llega a formarse, ésta nunca es gris sino roja, por lo tanto si ésta es persistente, llega a producir cambios hiperplásticos y fibrosos que pueden mas bien ser considerados como cicatriciales.

ANALYSIS OF ONE THOUSAND CONSECUTIVE AUTOPSIES:

WITH REFERENCE TO THE INCIDENCE OF TUBERCULOSIS IN THE DIFFERENT ORGANS.

By J. G. Adami, M.D. (Cantab.), F.R.S., and John McCrae, M.B., M.R.C.P. (Lond.).

In 1000 cases, evidence of tuberculosis, past or present, existed in 417, or 41.7 per cent. This probably represents a little less than the urban average for a Canadian city: it is considerably lower than many percentages that have been given for European cities, but it is based on exactly similar findings, so that it is directly comparable with these figures. Sources of error exist in our series, but we think they all tend to minimize the real figures; for example, there are undoubtedly small foci in glands or elsewhere that pass unnoticed, and there are many cases of puckering and fibrosis of the apex of the lungs which are probably tuberculous, but which we have considered as unproved, and have, therefore, not included.

The 417 cases fall into natural groups, which we shall discuss separately; certain general conclusions we shall make the subject of further reference.

Our groups are as follows:

1. Healed—151 cases: these are cases where the lesion exhibits calcification and fibrosis, with no caseous material or other evidence of latent or active disease.

2. Latent—93 cases: these show caseation, are apparently quiescent, and are localized.

3. Early Active—22 cases: in these there is evidence of the disease becoming active from a latent site, but its progress at the time of death was inconsiderable.

4. Generalized—43 cases: this type is seen oftenest in the young, and includes those cases which show a diffuse infection of many organs. It includes cerebral and meningeal tuberculosis.

5. Pulmonary—85 cases: in these the disease is mainly of the lungs, although it may terminally be in many other organs.

6. Tuberculosis of Bones—13 cases, in which the disease has primarily been in the bones or joints, whatever be the final dissemination of it.

7. Genito-Urinary Tuberculosis—10 cases: although the disease is

manifest elsewhere, the genito-urinary system shows the most advanced and most important lesions.

1. Obsolete or Healed Tuberculosis (151 Cases).

It has been considered that calcification in a situation that may reasonably be a likely site for tuberculosis, represents a healed lesion, provided that no obvious evidence exists to indicate a simpler origin of the lesion. If any caseation existed in a nodule, as well as calcification, the lesion was not counted as healed, but as latent; in the lung, no note was taken of simple puckering of an apex or of both apices, even though there was fibrosis of some slight depth; yet a fibroid nodule of sufficient size (say, 1 cm. diameter) in the lung tissue was considered as healed tuberculosis. It need scarcely be mentioned that it is often a difficult matter to say whether a nodule in a thickened pleura be pleural or pulmonary in origin, and in these cases the opinion of the dissector must be followed.

In 1000 autopsies healed tuberculosis, without progressive tuberculosis elsewhere, was found 151 times—78 in males, 73 in females. The average age of the subjects was 46.2 years, though, naturally, no idea can be formed of the age at which the lesion had become healed. It is worthy of note that as many as 4 healed lesions existed in 3 cases, 3 healed lesions in 14, and 2 in 26 cases.

Lungs.—The most frequent site was the lung, it being involved in 100 cases. The left was found the site of lesion in 65, the right in 62. In 72 cases the lung alone was involved. The upper lobes were affected by far the most frequently, and in the following number of cases: upper left, 56; upper right, 48; lower left, 8; lower right, 8; middle right, 5. When only one lesion was found, it was in the left apex in 37, in the right in 28; simultaneous lesion of both apices was found in 16. It will be noted that in this series the left lung predominates in frequency, contrary to the general belief.

Lymph-nodules.—The thoracic glands were involved in 45 cases, the majority of which occur, it must be said, in the later cases, when more attention was paid to this point than in the earlier years. The group mostly involved was that at the lung root (peribronchial), 38 times. The mass below the bifurcation of the trachea was involved 9 times; it was this group especially which escaped notice in the earlier years. Where only a single site was found, it was 23 times in the lung-root group. The abdominal groups of lymph-nodes were found to be the seat in 12 cases, the mesenteric groups giving 8 of these.

Sites of Single or Multiple Lesions.—Lung, 72; peribronchial nodes, 23; lung and peribronchial nodes, 10; pleura, 7; peritracheal nodes, 3; with peritracheal, 2; with peribronchial and mesenteric, 2; with liver, 2; with spleen, 1; with pleura and peritoneum, 1; with retroperitoneal, 1;

with peribronchial, peritracheal, and periportal nodes, 1; with spleen and liver, 1; with mesenteric nodes, 1; with peribronchial and periportal nodes, 1; with pleura, 1; with pleura and mesenteric nodes, 1.

Peritoneum, 2; periportal nodes, 1; adrenal, 1; peribronchial nodes and liver, 1; peribronchial and peritracheal nodes, 1; peritracheal nodes and pleura, 1.

2. Obsolescent or Latent Tuberculosis (93 Cases).

These cases show caseous or calcareocaseous foci, without evidence of active spread of the disease from them. Fifty-nine cases were males, 34 females, and the average age was 38.7 years. The lungs were involved in 72, the thoracic nodes in 35, the abdominal nodes in 6, the cervical nodes in 2. The spleen was affected in 6, the liver in 5, the pleura in 4, the peritoneum in 3, the kidney in 1, the epididymis in 1, the pericardium in 1. The lungs were the only site of disease in 46; in these 46 the right lung was involved 30 times; the left, 26; and both lungs, 10 times. When the lesion was confined to the apices, the right was affected in 14; the left in 10; both in 7.

Of the 72 cases in which the lungs were involved, the right was affected in 42; the left in 44; the right apex alone in 17; the left apex alone in 19; both apices in 10. The upper and lower lobes on the same side were the site of the disease twice on each side; only once was there a bilateral infection of the lower lobes as the sole lesion. The picture clinically familiar, of two apices, and the apex of the lower lobe of the side first affected, was seen only once. Its infrequency is doubtless due to the comparative rarity with which three-lesion tuberculosis becomes healed or latent. Single lesions of the lung in sites other than the apex were rare: the left lower lobe was affected 4 times, the right lower lobe 3 times, and the right middle lobe but once. The combination of lungs and thoracic nodes was common—18 cases; the lungs and abdominal nodes occurred but twice.

Single lesions of organs other than the lungs and lymph-nodes are also infrequent; we found the disease so situated in the liver once, in the kidney once, in the pleura twice. A number of combinations of organs also occurred infrequently, as follows: lungs, thoracic and abdominal nodes, 1; lungs, thoracic and cervical nodes, 1; thoracic and abdominal nodes, 1; thoracic nodes and epididymis, 1; lung and pericardium, 1; thoracic nodes and spleen, 2; cervical nodes and liver, 1; lung with pleura, 1; with peritoneum, 1; thoracic nodes with peritoneum, 1; spleen and liver, 1; spleen, liver, thoracic nodes, and lungs, 2; pleura, peritoneum, spleen, and thoracic nodes, 1.

Relation of Pleural Adhesions to Healed and Latent Tuberculosis.—For the purpose of this paragraph we have combined the cases of healed and latent disease, with the following result:

In 244 cases of latent and healed tuberculosis pleural adhesions were present in 178—nearly 73 per cent. In 24 cases tuberculosis existed in the lungs and no adhesions were present. In 11 cases tuberculosis existed in the thoracic nodes and no adhesions were present. In 6 cases tuberculosis existed in the lungs and thoracic nodes and no adhesions were present—which give a total of 41 cases with thoracic tuberculosis but without pleural adhesions. Further, 9 cases of lung tuberculosis showed adhesions, but elsewhere than the tuberculous disease. Thus, out of 239 cases of early tuberculous infection, 50 cases of thoracic tuberculosis show no direct relationship between the lesion and pleural adhesions.

The Site of Early Tuberculous Infection.—From the combined healed and latent lesions we found that, of 244 cases, the lung was the site of lesion in 172 (70 per cent.). Where there was but one lesion in an upper lobe, this occurred in the left upper lobe 75 times, in the right 65 times, again indicating a finding at variance with the generally accepted idea.

In 172 cases of lung involvement the left lung was affected in 108, the right in 103. Where the disease was in the apices, the left apex alone was affected in 56, the right in 45; both apices were affected in 26. In sites other than the lungs the thoracic nodes were affected in 80 (33 per cent.), the abdominal nodes in 18 (7.3 per cent.); the cervicals were observed only twice, a figure which indicates, we fear, a laxity of observation. The liver was involved 12 times (4.8 per cent.); the pleura, 11 (4.5 per cent.); the spleen, 8 times, and the peritoneum, 5.

Summary of Healed and Latent Tuberculosis.—Of 417 persons dying with evidence of previous or existent tuberculosis, 244 showed that the disease had been brought to a standstill; thus, 58.5 per cent. of infected cases had successfully met the invasion, and 36 per cent. of the infections had been actually cured.

3. Early Active Tuberculosis (22 Cases).

These are divisible at once into:

1. Meningeal cases, in which a latent site in the body had apparently set free its bacteria, and infection of the meninges had followed: 7 of these cases were found.

2. True early active cases, in which a latent site had suddenly become once more active; death in these cases occurred from some other cause, and the tuberculosis is but an accidental finding. Of the 15 cases so described, the disease was very slightly advanced in 13, and considerably in 2, yet not sufficiently to make us class it with the other types of tuberculous infection. The form nearly always found was that a few fresh miliary tubercles were found in the vicinity of an old caseous focus.

4. Generalized Tuberculosis (43 Cases).

This interesting group of cases gave an average age of 19.3 years. The following organs were most often involved, in order of frequency: lungs, 41 (95 per cent.); lymph-nodes, 35 (81 per cent.); some one or more of the serous surfaces, 28 (65 per cent.); spleen, 28; liver, 27 (63 per cent.); intestines, 23 (53 per cent.); meninges, 21 (49 per cent.); kidneys, 21; adrenals, 10 (23 per cent.); and brain, 6 (14 per cent.). The only cases which did not show the lungs involved were a coroner's case, with very brief notes, and an acute case when suppuration of the glands was followed by miliary tuberculosis of the spleen and kidneys.

Sites of Involvement.—*Lymph-nodes*, 35 cases: Thoracic, 33; thoracic alone, 17; thoracic and abdominal, 16; abdominal, 18; abdominal alone, 1; axillary, 1; inguinal, 3; cervical, 5. The thoracic duct was involved once.

Of 43 cases, the lymph-nodes were the site in 38. The alimentary canal in about half; the small intestine was affected thrice as often as the large. The serous surfaces were affected as follows; oftenest, pleura and peritoneum, then peritoneum alone, then pleura alone. The heart valves were found involved once.

Six cases had tuberculous brain tumor, and all, save one, had tuberculous meningitis.

Alimentary tract, 23 cases: Stomach, 1; small intestine, 21; large intestine, 7; rectum, 1. The stomach and ileum were affected in 1, the small intestine alone in 15, the small intestine with colon, 4, with colon and rectum, 1. The colon was affected alone twice. All lesions were ulcerative.

Serous surfaces, 28 cases: All 3 were affected in 2; the pleura and peritoneum in 12; the pleura and pericardium in 2; the pleura alone, 5; the peritoneum alone, 7; and the pericardium was not found affected alone.

Other organs, not given above, were affected in the following numbers of cases: heart muscle, 2; bone, 2; bladder, 2; prostate, 2; ovary, 2; Fallopian tube, 2; and the following once each: heart valve, pancreas, thymus, diaphragm, seminal vesicle, vas deferens.

Distribution in Lungs.—All 5 lobes were involved in 26 cases, three lobes in 3, two lobes in 5, and one lobe in 7. Five cases showed cavitation; 14 cases showed miliary distribution only; 13 cases showed caseous and miliary foci (in 11 of these there was but one caseous focus); 5 showed caseous foci only; 2 cases showed apparently healed calcareous areas, and 2 showed bronchopneumonia only.

Relation of Pleural Adhesions.—Of the 41 cases with infection of the lungs, 18 showed bilateral adhesions, 7 left-sided and 7 right-sided adhesions; 9 cases showed no adhesions despite lung involvement (the ages

of these 9 averaged 12.4 years, the oldest being thirty-two years), and in 1 case the adhesions were on the side opposite to the lung lesion.

Types of Disease.—Four cases showed essentially a serous surface type of involvement.

Of the 6 cases with brain tumor (tuberculoma) all save one showed involvement of the meninges.

Meningeal.—In our entire series of tuberculosis 30 cases of tuberculous meningitis were found; 23 of these, (76 per cent.) had active tuberculous foci elsewhere, and 21 (70 per cent.) had a generalized tuberculosis with many lesions. This indicates the extreme likelihood that a tuberculous meningitis is but a local expression of a wide-spread infection, and suggests, further, the hopelessness of any operative procedure in a large majority of all cases of the disease.

5. Pulmonary or Ulcerative Tuberculosis of the Lungs with Cavitation (85 Cases).

These constitute the actual cases of phthisis, and showed an average age of 36.6 years, and consisted of 57 males and 28 females. Of the 85 cases, 4 were of the fibroid type, 10 had developed amyloid disease of some organ or organs; 4 cases showed pneumothorax, 2 empyema, 2 had perforation of a tuberculous ulcer of the bowel, and 4 cases had diabetes.

Lungs.—The site of the cavitation is stated in but 79 of the cases. Cavitation affected the left upper lobe 57 times, the left lower 22, the right upper 54, the right middle 16, and the right lower 15 times. The cavities were generally multiple, as follows:

All five lobes were affected 5 times.

Four lobes 6 times, *i. e.*, three right lobes and upper left, 4; two left lobes and two right, 2.

Three lobes 6 times, *i. e.*, two left lobes and right upper, 4; two right lobes and left upper, 2.

Two lobes 30 times, *i. e.*, both upper, 16; two left, 7; right upper and middle, 2; right upper and lower, 2; right upper and left lower, 2; left upper and right lower, 1.

One lobe 26 times, *i. e.*, left upper, 13; right upper, 11; right middle, 2.

Pleura.—Of the 85 cases, 83 showed pleural adhesions, 73 bilateral, 6 on the right side only, and 4 on the left. The pleura was noted to be definitely tuberculous in 28 cases.

Larynx, Etc.—Twenty-five cases showed tuberculosis of the upper air-passages. Pharyngeal tuberculosis was seen in 2 cases; the epiglottis was affected in 8; tuberculous laryngitis or tracheitis was seen in 14; tuberculous bronchitis in 15.

Alimentary Tract.—Fifty cases were thus affected; practically always

the disease was ulcerative. The regions were attacked as follows: Stomach, 1; small intestine, 48; large intestine, 35; appendix, 8; rectum, 8; the small intestine alone was affected in 13; the large intestine alone in 2.

TUBERCULOUS INFECTION OF OTHER ORGANS.—*Lymph-nodes.* The thoracic nodes were noted as affected in 40, the abdominal in 19, the cervical in 5. The two former are probably much understated, as, with the presence of a large cavity, the lesser manifestations of the disease are apt to pass without comment.

The lymph-nodes, by groups, were affected as follows: Cervical, 5; peribronchial, 28; peritracheal, 4; mediastinal, other than the above, 8; mesenteric, 17; retroperitoneal, 2. Of the 17 infections of the mesenteric nodes, 15 occurred with bowel ulceration; of the 2 without bowel involvement 1 was calcareous and 1 caseous. The 2 cases of involvement of retroperitoneal nodes were free from intestinal lesion.

The *spleen* was affected 17 times; the *peritoneum*, 17; the *liver*, 14; the *kidney*, 14; the *meninges*, 5 times; *adrenals*, 4; *pericardium*, 3; *bones* (rib), once; *pancreas*, *thymus*, and *diaphragm*, once each. In the genito-urinary tract the *prostate* was infected 4 times, the *seminal vesicles* 3 times, the *vas deferens* twice, the *bladder* twice, the *testis*, *ureter*, and *epididymis* once each.

6. TUBERCULOSIS OF BONES.

Thirteen cases, average age, twenty-six years. Males, 7; females, 6. This series is too small to be instructive. In 9 cases disease of the vertebræ, oftenest the lumbar region, was present; the hip-joint was next in order of frequency. Sinus existed in 8 cases, psoas abscess in 5, prevertebral abscess in 2. In 8 the lungs were affected, in 3, the pleura, in 1, the pericardium. The thoracic glands were involved 6 times, the abdominal glands twice, the inguinal once. The spleen was thrice involved, the adrenals twice, the liver but once.

7. GENITO-URINARY TUBERCULOSIS.

In 10 cases, of whom 6 were males and 4 females, the average age was 31.9 years. In every case tuberculosis existed elsewhere: in 3, the primary site appeared to be in the lung, ovary, and mesenteric glands respectively; the kidney was diseased in 9 cases, 5 of which were bilateral and 4 unilateral. The ureter was tuberculous in 4, the bladder in 7, the prostate in 4. The vas deferens in its course was affected once, the seminal vesicles 4 times, the epididymis 3 times, the testes once. Twice was the ovary affected, and twice the Fallopian tube, and the uterus and vagina once each. In 8 the lungs were diseased, 4 times bilaterally; the spleen was affected 4 times, the

liver 3 times, the adrenal once, the intestines thrice, the meninges once, the thoracic glands never, and the abdominal glands twice. In one of these the abdominal glands seemed to be the earliest site, as is mentioned before.

Analisis de mil Autopsias Consecutivas en Montreal con Referencia á la Incidencia de la Tuberculosis en los Diferentes Organos.—
(ADAMI Y MCCRAE.)

Mil autopsias; tuberculosis presente ó posterior en 41.7 per cent. de los casos (417 casos).

Los cambios anatómicos sobre los cuales se basa, esto es, cuales de las lesiones ligeras son concideradas como tuberculosis y cuales no lo son.

Los Grupos: (*a*) Curados, 151 casos. (*b*) Latentes, 93. (*c*) Activas, pero ligeras, 22. (*d*) Generalizadas, 43. (*e*) Pulmonares (Tisis), 85. (*f*) Tuberculosis de los huesos, 12. (*g*) Genito-urinaria, 10.

(*a*) Curados: Distribución con relación al sexo, edad, número de lesiones. Lugar de la infección: El pulmón izquierdo predomina. Glandulas, grupos de éllas afectadas. Relación de la tuberculosis obsoleta a las adhesiones de la pleura.

(*b*) Latente: Definición (presencia de degeneración caseosa). Sexo, edad, número de las lesiones y el lugar de éllas. Relación entre la tuberculosis obsoleta y las adhesiones de la pleura. Lugar de la primera afección tuberculosa. Sumario de los casos curados y latentes de tuberculosis y relación de estos al numero total (58.5 per cent.) de los casos resistieron con exito a la invasión).

(*c*) Primeramente activa:

1. Tuberculosis de las meninges en las cuales la enfermedad no fue generalizada (7).
2. Casos anteriores en los cuales la tuberculosis se encontró accidentalmente, y que el paciente sucumbió á causa de otra enfermedad (15).

(*d*) Generalizada:

Organos afectados. Lugar de la infección: nudos linfaticos, el aparato digestivo, superficies serosas, otros organos.

Distribución de la enfermedad en los pulmones, relación de éstas á las adhesiones de la pleura. Afección de las meninges.

(*e*) Tisis:

Distribución de la afección en los pulmones, la laringe, el aparato digestivo. Relación a las adhesiones de la pleura. Lesiones en los otros organos.

(*f*) Tuberculosis de los huesos, pequeñas series.

(*g*) Genito-urinaria. Pequeñas series. Organos afectados.

Eine Analyse von 1000 aufeinanderfolgenden Autopsien, mit Bezug auf das Auftreten von Tuberkulose in den verschiedenen Ursprungs-Erscheinungen.—(ADAMI UND MCCRAE.)

Tausend Fälle zur Autopsie. Tuberkulose verflossen oder anwesend in 417 Fällen.

Die anatomischen Veränderungen auf welchen es basiert, d. h. welche leichte Verletzungen als tuberkulös angesehen werden, und welche nicht.

Die Gruppen:

(*a*) Geheilt: 151 Fälle. (*b*) Latent: 93. (*c*) Aktiv aber leicht: 22. (*d*) Allgemein: 43. (*e*) Lungen (Schwindsucht): 85. (*f*) Knochentuberkulose: 12. (*g*) Geschlechts-Urintrakt: 10.

(*a*) Geheilt: Verteilung in Bezug auf Geschlecht, Alter, Zahl der Verletzungen. Sitz: Lungen (vorwiegend die linke). Drüsen-Gruppen involviert. Beziehungen von ausgeheilter Tuberkulose und Pleuralverwachsungen.

(*b*) Latent: Definition (Anwesenheit von Verkäsung). Geschlecht, Alter: keine. Beziehungen von geheilter und latenter Tuberkulose zu Pleural-Verwachsungen. Die Eintrittsplätze der frühen tuberkulösen Infektion. Summe der geheilten und latenten Tuberkulose in Beziehung zur Gesammtzahl der Fälle. (58.5 Prozent der Fälle waren der Invasion erfolgreich begegnet.)

(*c*) Frühzeitige aktive:

1. In der Gehirnhaut, wo die Krankheit nicht allgemein war, 7.
2. Frühzeitige Fälle, wo Tuberkulose zufälligerweise bei solchen gefunden wurde, die an anderen Krankheiten starben.

(*d*) Organe in Mitleidenschaft gezogen.

Sitz: Lymphknoten; Verdauungstrakt; seröse Oberflächen; andere Organe. Verteilung in den Lungen; Beziehungen zu Pleura-Verwachsungen. Gehirnhäute in Mitleidenschaft gezogen.

(*e*) Schwindsucht: Verteilung in Lungen, Kehlkopf, Verdauungstrakt. Beziehungen zu Pleura-Verwachsungen. Verletzungen anderer Organe.

(*f*) Knochentuberkulose: Kleine Serien.

(*g*) Geschlechts-Urintrakt: Kleine Serien. Organe in Mitleidenschaft gezogen.

ORGANIZED PLEURAL ADHESIONS AND THEIR RELATIONSHIP TO TUBERCULOSIS:

BASED ON AN ANALYSIS OF 1374 CONSECUTIVE AUTOPSIES.

By A. R. Landry, M.D.,

From the Royal Victoria Hospital, Montreal.

There has been very considerable discussion, of late years, regarding the diagnostic value of acute pleurisy as an indication of tuberculosis, there being those that hold that the majority of cases are tuberculous, while others dispute the point. Pleural adhesions, it need scarce be said, have their starting-point in an acute or subacute pleurisy, and, following the suggestion of Professor Adami, I made a full analysis of 1374 consecutive autopsies performed at the Royal Victoria Hospital, to determine, as far as the material permitted, the incidence of systemic tuberculosis and other relationships to pleural adhesions.

That material was peculiarly favorable for the purposes. In the first place, it constitutes a larger series than any I have been able to encounter in the literature. The number of autopsies performed at the Royal Victoria Hospital is not great, averaging less than three a week, so that there is leisure for thorough study and record of individual cases; the whole series has been performed under the supervision, and according to the methods, of one pathologist; these methods have, from the first, involved a conscientious tabulation of every recognized deviation from the normal, common conditions, such as pleural and peritoneal adhesions, being recorded with as much care as are the more obvious causes of death. The notes are made by a student or interne at the time of autopsy, and then dictated in a definite order to a stenographer. The material is that of a large general city hospital, consisting in the main of medical and surgical cases. The notes to be made regarding that material, as an adequate or defective index of Canadian morbidity, are that the number of infants and children under twelve, admitted to the hospital, is well below the average of the general population; that chronic long-standing cases of disease gain entrance to the wards with difficulty, and that cases of active pulmonary tuberculosis are not knowingly admitted into the medical wards, save rarely, and then, as it were, under protest. The majority of cases coming to autopsy are derived from the medical and surgical wards: the gynecological, ophthalmo-

logical, and laryngological beds supply very few. In all these respects the hospital is a typical city hospital; the majority of patients come from the city of Montreal, but a large minority gain entrance from the surrounding country. Some come from distant parts of Canada, and from across the border from the neighboring States of Vermont, New York, and New Hampshire. Lastly, as a seaport town, there is somewhat above the usual percentage of "outlanders" of both sexes.

In 1895 there were admitted into the Royal Victoria Hospital 1841 patients, and in 1907, 4044 were admitted. In 1907 the average number of patients in the hospital per diem was 224, of which 74 were medical, 95 surgical, 28 gynecological, and the remaining 27 are accounted for in the ophthalmological, laryngological, and otological wards.

I have carefully gone through the notes of the 1374 cases, and before discussing my results it is necessary to call attention to the limits to be placed on the accuracy of the recorded results. In the first place, only organized adhesions are taken into account. Of these, one group is not included in the table, and this because I could not convince myself that they had always been noted: I refer to interlobar adhesions. The time for viewing pleural adhesions in general is when making the preliminary inspection of the thorax. When interlobular adhesions alone are present, these may easily be overlooked at this period and fail to be recorded later. Secondly, it must be kept in mind that the diagnosis of tuberculosis has been based purely on naked-eye examination. It is true that, in a large percentage of cases, in the routine examination of sections of, on the average, eight major organs of the body, the diagnosis has been confirmed under the microscope, and again in a smaller proportion by bacteriological methods. This table, however, is based upon gross appearances. Those tubercles, invisible to the naked eye, in the cervical and other lymph-glands, have not been taken into account. Similarly, mere puckering of the apex of the lung with no other gross sign of tuberculosis has been ruled out from our main tables of tuberculosis, unless associated with this there were definite underlying calcified or fibroid tubercles. The minute subpleural, fibroid, tubercle-like bodies, which Hodenpyl regards as true arrested tubercles, have also been placed under a separate column. We believe that both of these conditions are indications of old pleural tuberculosis, but the demonstration not being absolute, we have thought it wiser to place these cases in a definite category, along, we would add, with those cases in which rare solitary, small, shot-like calcareous bodies in the liver or spleen have been the only tubercle-like lesions discovered.

Yet another point deserves attention. It is evident and natural that certain observations, at first made perfunctorily, are later pursued more keenly, as their importance becomes more fully realized. Thus, for example,

in the early half of this period, when attention had not been drawn to the frequency of a solitary focus of tuberculosis in the peribronchial glands, or more particularly in the gland clusters at the bifurcation of the trachea, it is probable, nay, certain, that the presence of the disease there, while frequently recorded, was not infrequently overlooked. To the more frequent detection of obsolete tuberculosis in these regions we would, in the main, ascribe the difference between our figures and those contributed to this Congress by Dr. J. McCrae. Our series embraces some 400 more recent reports, which are not included in his analysis. It goes without saying that our figures are well below what we are convinced is the actual amount of tuberculosis in our material. Lastly, the notes have permitted us to recognize the following main orders of pleural adhesions:

(1) Generalized, affecting one or other lung.
(2) Scattered or sporadic.
(3) Apex free, but adhesions in a few cases below and in front.
(4) Adhesions separated with difficulty.
(5) Those that the slightest touch would destroy.

Next, as to the results obtained.

I. Frequency of Old Pleural Adhesions.

Of the 1374 cases, 990, or 72.1 per cent., are recorded as exhibiting adhesions of one or other degree; 384, or 27.8 per cent., as free from adhesions. These figures, I may note, are closely in accord with those determined by Lord, of Boston. In a smaller series of 215 autopsies (less than one-sixth of ours) he found 74.4 per cent. of adhesions. In other words, in the north-eastern portion of North America it may safely be laid down that seven out of ten adults exhibited indications of a previous pleurisy.

II. Age Incidence.

I hope later to publish this table in full. Here I would merely quote McCrae's figures, viz., that the average age of cases coming to autopsy was forty-six for the first 1000 cases, and there is no reason to believe that our next 374 cases would change this average.

III. Relationship of Systemic Tuberculosis to Old Pleural Adhesions.

Of this series of 1374 cases, 558, or 40.6 per cent., afforded definite macroscopical evidence of tuberculosis in the thoracic cavity. Sixty-eight other cases showed evidence of tuberculosis, according to our classification, either in the mesenteric glands, liver, spleen, or bones.

Thus, summing up, we have, of undoubted tuberculosis in the thorax, 558 cases (40.6 per cent.); cases showing tuberculosis elsewhere than in

the thorax, 68 cases (4.9 per cent.); or 626 cases of tuberculosis in 1374 cases (45.5 per cent.).

If fibrosis of the apex be counted as tuberculous (89 cases), we then have 715 cases of tuberculosis, a percentage of 52.

Here it must be understood that we deal with obsolete or obsolescent tuberculosis, or again with progressive tuberculosis of a more chronic type. It is scarcely necessary to point out that acute miliary tuberculosis, devoid of any sign of an older focus of primary infection, is not here taken into consideration, and that because an acute tuberculosis cannot account for old pleural adhesions.

(*A*) *Cases of Tuberculosis (Other Than Acute Miliary), Showing no Old Pleural Adhesions.*—Of the 384 cases showing no adhesions (27.8 per cent.), evidence of tuberculosis was found in 103, or 26.8 per cent. of the cases. In other words, in cases without adhesions, 26.8 per cent. have suffered, to some degree, from tuberculosis. Of these, the site of the tuberculosis was in the thorax in 82 cases (21.3 per cent.), not including 9 which showed merely apical fibrosis, and the tuberculosis was elsewhere (alone) in 21 cases.

In other words, as might be expected, not all cases of thoracic tuberculosis are accompanied by pleural adhesions.

It must be obvious to all that the 27.8 per cent. does not represent merely those that never suffered from pleurisy, for there may be perfect resolution of an acute pleurisy, no adhesions being formed; nay, more, we have to recognize, and in this view we are confirmed by experiments on the dog, that organized adhesions may undergo eventual absorption.

(*B*) *Cases of Tuberculosis Accompanied by Old Adhesions.*—Of the 626 cases of tuberculosis in 1374 cases (45.5 per cent.), 523 showed adhesions, or 83.5 per cent., as against 1000 cases of adhesions, where 523 cases showed tuberculosis variously distributed (52.3 per cent.).

If, on the one hand, 103 cases showed evidence of tuberculosis with no coincident adhesions, there were, on the other hand, 523, or 83.5 per cent., of cases of tuberculosis with adhesions, or, roughly, *five cases of tuberculosis are accompanied by adhesions to every one that shows none.* The only figures bearing upon this point that I can refer to are those of Dr. J. McCrae, communicated to this Congress, based upon the first thousand of this series from which similar conclusions are drawn. Out of these 1000 cases, Dr. McCrae found 24 with pulmonary tuberculosis, 11 with tuberculosis of the thoracic lymph-nodes, 6 with tuberculosis of both lungs and thoracic nodes. He does not consider the cases in which the only recognizable tubercular lesions were outside the thoracic cavity. He concludes that out of 239 cases of early (or, more accurately, slight, obsolete, and latent) tuberculous infection, 50 cases show no direct relationship between the lesion and pleural adhesions, or, roughly, nearly one out of every five.

There is another and converse ratio to be determined, namely, the proportion of cases of old adhesions that afford coincident indications of tuberculosis in some region of the body. Of the total number of 990 cases of adhesions, 523 showed tuberculosis, or 52.3 per cent. Or, to put this clearly, while five out of every six cases of visible tuberculosis are accompanied by adhesions, only one out of every two cases of adhesions exhibits coincident tuberculosis.

This is a very striking result, and one that must be taken into serious account in the estimation of the diagnostic value of pleurisy in general. If we can draw any conclusion from the analysis, it is that there are two roughly equal groups of cases of pleural adhesions, and presumably, therefore, of pleurisy; one in which there is associated tuberculosis; the other in which all naked-eye indications of that disease are wanting.

How are we to harmonize these results with those that have been gained by clinicians and bacteriologists bearing upon the tuberculous nature of the majority of cases of clinically recognizable acute pleurisy? I am of the opinion that if they cannot be reconciled, at least, an explanation is possible of the divergence.

Let us note, first, that clinically recognizable acute pleurisy is a relatively rare event, compared with the occurrence of pleural adhesions. To give an example, at the Massachusetts General Hospital, Lord, out of 18,543 patients examined, found that acute pleurisies had been diagnosed only in 2.4 per cent. of the cases. Osler quotes a series of 19,396 cases at the Pennsylvania General Hospital, as affording 505 cases of this condition, or 2.6 per cent. Similarly, Wurzburg clinics, in thirteen years, had an incidence of 3.4 per cent., although the Charité at Berlin, in eight years, gave 9 per cent. Compare these figures with our 72 per cent. of observed old adhesions in 1374 autopsies. Clinical notes are generally silent where the adhesions over one or both lungs are dense or universal.

The conclusion is inevitable that only a small proportion of cases of pleurisy in the acute stage yield clinical symptoms. It is this proportion that is represented by the cases of acute pleurisy with effusion. We must freely accept such figures as those of Aschoff, that 68 per cent. of the animals inoculated from cases of serous pleurisy succumbed to tuberculosis, and even those of Le Damany, that 86 per cent., or even 96 per cent., of the exudates in such cases induce tuberculosis in the animals of the laboratory. But, in addition, there is a different series of cases of acute pleurisy, which is not of tuberculous origin, and is not necessarily accompanied by clinical symptoms.

It might be urged that these cases, or a considerable proportion of them, of adhesions without recognizable tuberculosis, are instances of old primary pleural tuberculosis without lesions elsewhere. That such primary pleural

tuberculosis exists is well ascertained. But, on the other hand, such evidence as we possess indicates that this is a relatively rare condition. It cannot be invoked to explain this large series of cases.

Lastly, we must freely admit that the macroscopical test is unreliable for the determination of the existence of tuberculosis within the organism. We may assuredly state that, of the 467 cases which showed adhesions but no recognized tuberculosis, some focus of tuberculosis was present in a large proportion. I would urge, however, that even if this be so, it does not explain the adhesions. Dr. J. McCrae's studies show clearly that the slighter and the more latent or obsolete the tuberculosis in the thorax, the less is the percentage of cases of adhesions, and when the tuberculous focus is extrathoracic, still less frequent are the cases of adhesions, otherwise the presence of minute isolated foci of tuberculosis cannot be invoked to explain the often extensive adhesions found in this series of cases. It is, we think, impossible to escape the conclusion that there are two approximately equal orders of cases of pleural adhesions,—one of tuberculous, the other of non-tuberculous, origin,—a conclusion which, after all, is the more rational, the more in line with our experience of chronic inflammation affecting other regions of the body.

Incidencia de la Pleuresia Crónica en 1400 Autopsias Consecutivas y su Relacion con la Tuberculosis.—(LANDRY.)

Este articulose refiere á 1400 autopsia hechas consecutivamente en el Royal Victoria Hospital de Montreal. Se presentará una estadistica mostrando la frecuencia de la pleuresia crónica, el lugar mas favorito de la enfermedad, la asociación de ésta con otras enfermedades del pulmón, del corazón, de otras cavidades serosas, del higado, del bazo, de los riñones, etc. Detalles sobre la historia personal del paciente, y de la familia, especialmente bajo el punto de vista de la tuberculosis y de otras enfermedades infecciosas. El termino medio de la edad al tiempo de la muerte es de 35 años y pacientes afectados de tuberculosis son tomados en el hospital tan poco como es posible.

THE FREQUENCY OF HEALED TUBERCULOSIS OF THE MESENTERIC GLANDS,

WITH PARTICULAR REFERENCE TO THE RELATIONSHIP BETWEEN HYALINE DEPOSITS IN THESE GLANDS AND THE HEALING OF TUBERCULOUS LESIONS.

By Aldred Scott Warthin, Ph.D., M.D.,
Professor of Pathology, University of Michigan, Ann Arbor.

For the last fourteen years I have given particular attention, in my autopsy work, to the examination of the mesenteric and retroperitoneal lymph-nodes, with especial reference to the hemal and hemolymph structures found in these regions. In the prosecution of these studies it has been necessary to examine microscopically many thousand lymph-nodes, primarily to determine the anatomical type of the given gland. During this detailed study a number of things worthy of note were observed, some of these bearing particularly upon the tuberculosis problem. One of the most striking of these observations is that relating to the constant occurrence, in the mesenteric and retroperitoneal lymph-nodes of adults, of small hyaline masses, and the possible interpretation of these as healed tubercles. If such an interpretation can be accepted, then the intestinal route of infection in tuberculosis is very common indeed, inasmuch as such evidences of its occurrence can be found in all adults.

Small masses or "droplets" of hyalin have been repeatedly described as occurring in senile and atrophic lymph-nodes. They stain bright red with eosin or a deep fuchsin-red with acid fuchsin in the Van Gieson's stain. They may occur in any part of the node, but are more frequently found in the cortex than in the medullary portion. Not infrequently they are found in the germ-centers, or in small collections of lymphoid cells suggesting germ-centers. They are usually round, sharply circumscribed, and may be wholly devoid of nuclei or may contain a few lymphocyte or connective-tissue nuclei according to their size. The larger the hyaline mass, the more likely it is to contain nuclei. In size they vary from minute points, two or three times as large as a lymphocyte, to small masses that may be seen distinctly with the naked eye.

Such hyaline masses differ from the diffuse hyaline change occurring in the stroma of atrophic glands, and can also usually be easily distinguished from hyaline blood-vessels. In serial sections such a distinction is easily

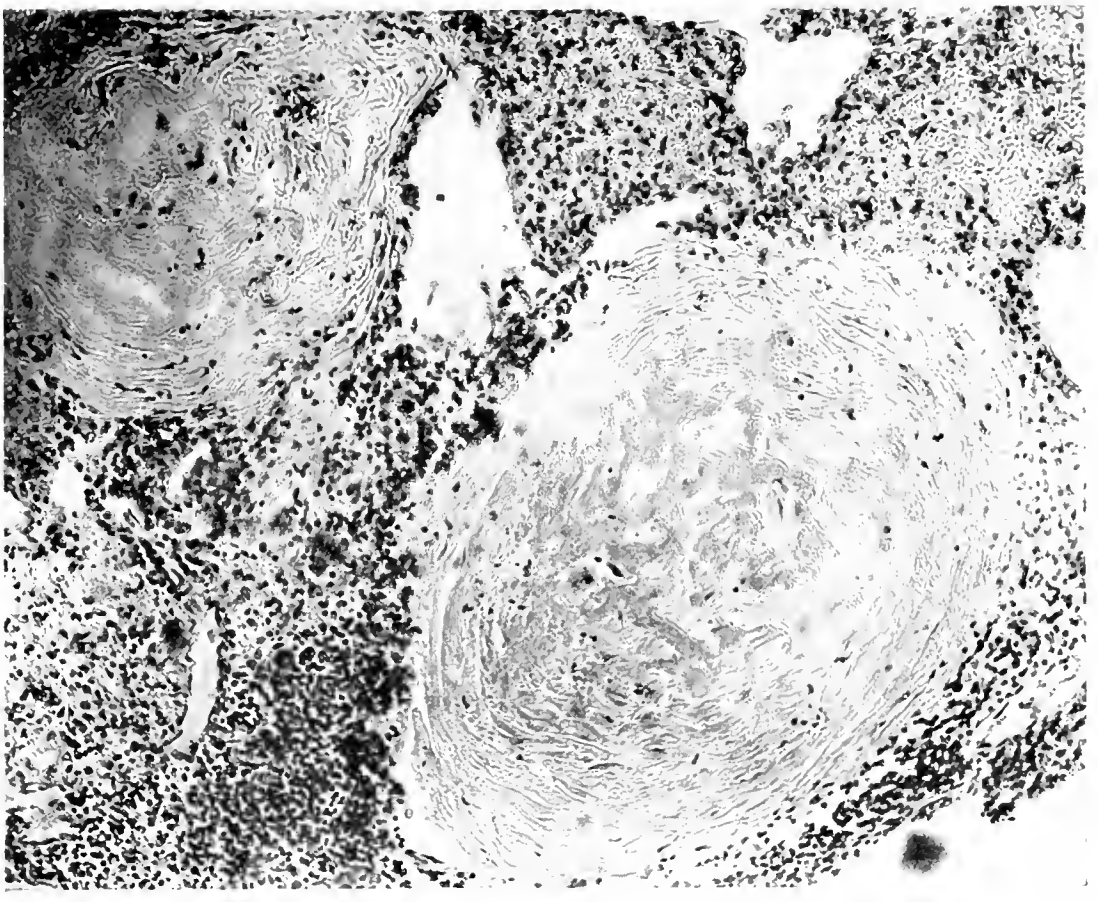


Fig. 1.—Primary miliary tubercles in mesenteric gland. Healing and beginning hyaline transformation.

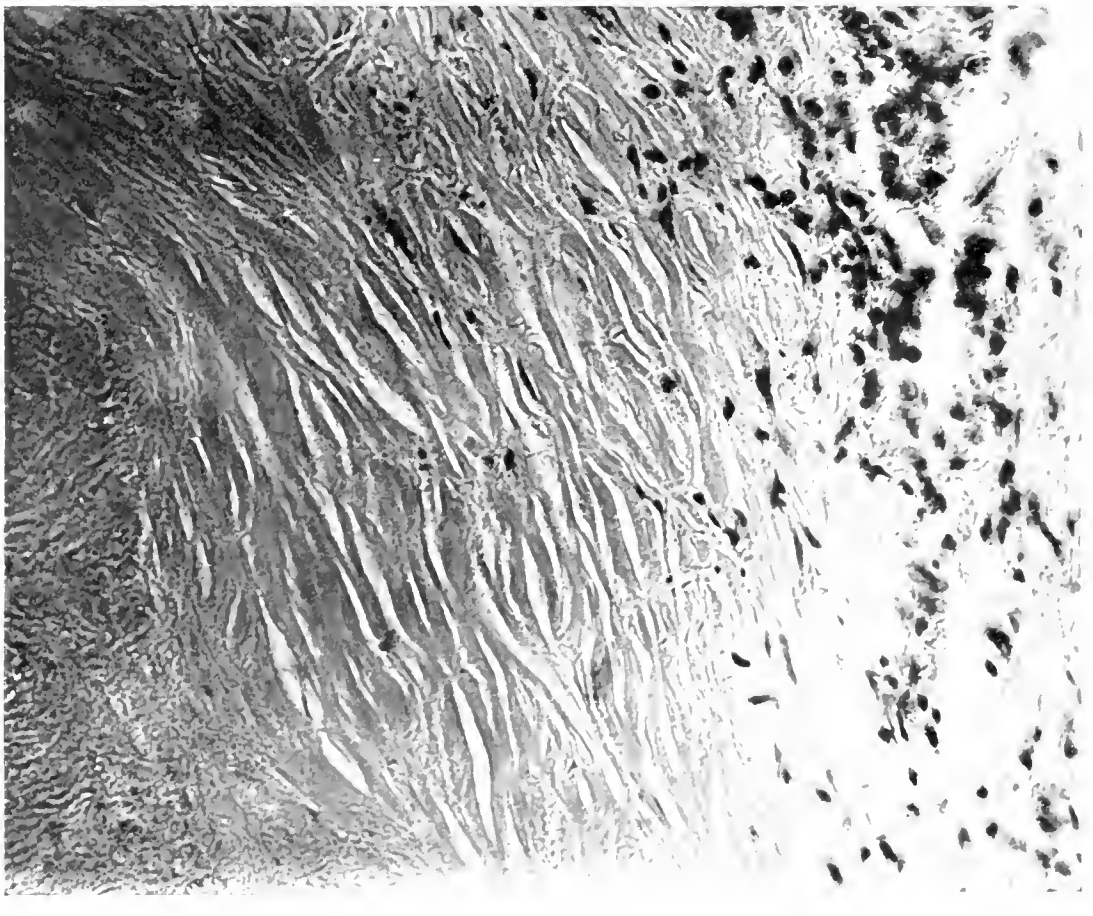


Fig. 2.—Edge of primary miliary tubercle of mesenteric gland. Showing hyaline transformation in its early stages.

made. They are often confluent; and often smaller hyaline droplets surround a larger hyaline mass. Small deposits of lime-salts are often found in the center of the larger hyaline masses, and often the center is finely granular and stains yellowish with the Van Gieson's. In sections treated for the iron-reaction (potassium ferrocyanid and hydrochloric acid) a distinct iron-reaction is often obtained in the center of the hyaline mass.

The larger hyaline masses stain more lightly than the small ones, and are less dense and refractive than the latter. The smallest ones have the highest refraction, stain more intensely, and give the impression of being older, contracted, or condensed masses of the same substance as the larger. The absence of nuclei in the smaller ones also bears out this view. Further, the larger ones (1 to 2 mm. in diameter) show varying stages of a process which can be no other than that of a progressive *organization of a lesion,* and the *hyaline transformation of the connective tissue replacing the lesion.* The hyaline masses are, therefore, *hyaline scars.*

The common interpretation accorded to the hyaline deposits in lymph-glands is that they are wholly of the nature of *retrograde changes,* and that they are associated especially with atrophy and fatty infiltration as an evidence of senile retrogression. In so far as the hyaline change in the stroma and reticulum of lymph-nodes is concerned, such a view is, I believe, correct; but in the case of the individual hyaline droplets and masses such an interpretation does not hold, for the reason that these occur at all periods of life, even in young people, totally unassociated with other retrograde changes. Instead of showing the latter, the glands containing the hyaline masses may present a condition of marked lymphoid hyperplasia.

In my first studies on the human hemolymph-nodes I was inclined to interpret these masses as representing a hyaline transformation of red blood-cells. This conclusion was largely due to the fact that iron-containing pigment could be found in some of the hyaline droplets. At the present time my view is that they represent healed lesions, these lesions being, *in the majority, if not in all cases, tuberculous in nature.*

1. In advanced cases of pulmonary tuberculosis the mesenteric and retroperitoneal glands constantly show miliary tubercles in various stages of epithelial proliferation, caseation, encapsulation, organization, and hyaline transformation; and in such cases all steps between the young miliary epithelioid tubercle and the small, deeply staining hyaline masses can be seen. In such cases there can be no doubt that the hyaline droplets are the end-results of the healing of tubercles. The stages may be expressed as follows: epithelioid cells, caseation, encapsulation, organization, contraction, condensation, hyaline transformation. Absolutely continuous stages may be seen in the same gland. The proof for the first point necessary to the establishment of our theory is easily obtained: these hyaline formations can result from the healing of small tubercles.

2. In my last one hundred autopsies, ten cases, showing no active pulmonary tuberculosis, but with thickened pleura at apices and calcareous nodules in bronchial glands, presented, in several mesenteric nodes, small miliary tubercles undergoing hyaline transformation. In some hyaline masses a minute caseous center, or a single giant-cell or a few epithelioid cells remaining, showed conclusively the tuberculous nature of the process. In a case of pernicious anemia, and in one of hepatic cirrhosis, active miliary tubercles were found in mesenteric nodes in association with miliary hyaline masses showing various stages of transformation from tubercles, while no tubercles could be found in any other part of the body. Primary tuberculosis of the mesenteric nodes must, therefore, be more common than is usually supposed, and may be found wholly independent of any intestinal lesion. In such cases healing of the tubercles may occur, and the end-result of such healing is the formation of hyaline droplets.

3. In the great majority of cases in which hyaline formations are found in the mesenteric nodes no active tubercles are found in the body, but the form of the hyaline droplet, its sharply circumscribed character, the evidences of a capsule, concentric arrangement, the occurrence of plasma-cells, the central non-hyaline or calcareous granular matter—all give abundant reason for assuming that they represent healed tubercles.

4. Such hyaline droplets are most common in the mesenteric, cervical, and bronchial nodes. In every adult body that I have examined they were present. In the axillary nodes they were very rare in my cases. In hundreds of axillary nodes examined microscopically in cases of carcinoma of the breast no hyaline droplets were found. In several cases of tuberculosis of the breast, the axillary nodes showed both tubercles and various stages of hyaline transformation of tubercles. They are more common in the inguinal nodes, and in one case were found in various stages of development in connection with miliary tubercles. In the tonsils they are extremely rare. In the sections from four hundred tonsils examined in this laboratory, tubercles and hyaline droplets were found only in two cases. It is certainly a very significant fact that the only hyaline droplets seen in any tonsils were in these two cases of tuberculous tonsils.

5. The argument may be brought forward that any lesion, characterized by active cell-death in a lymph-node, may on healing give rise to a hyaline formation. Such a possibility we must accept. Focal necrosis of a lymph-node due to diphtheria, typhoid fever, syphilis, chancroid, or other infections would, on healing, give rise to a focus of scar-tissue which would undergo a hyaline transformation. Accepting this as a definite possibility, the question then becomes one concerning the relative frequency of hyaline formations from these different processes. I have made especial investigations as to this point. In so far as diphtheria is concerned, the small foci of fatty

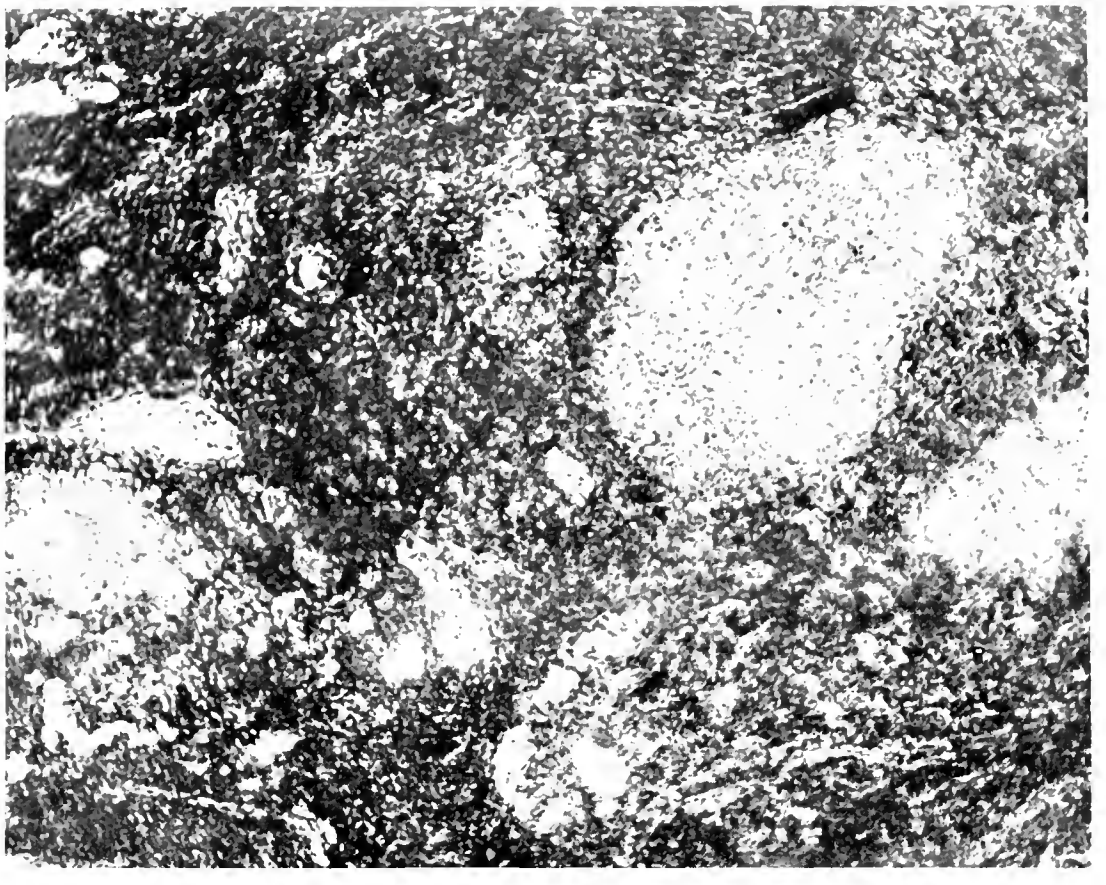


Fig. 3.—Miliary epithelioid tubercles and small hyaline healed tubercles. Mesenteric gland in case of pulmonary tuberculosis.

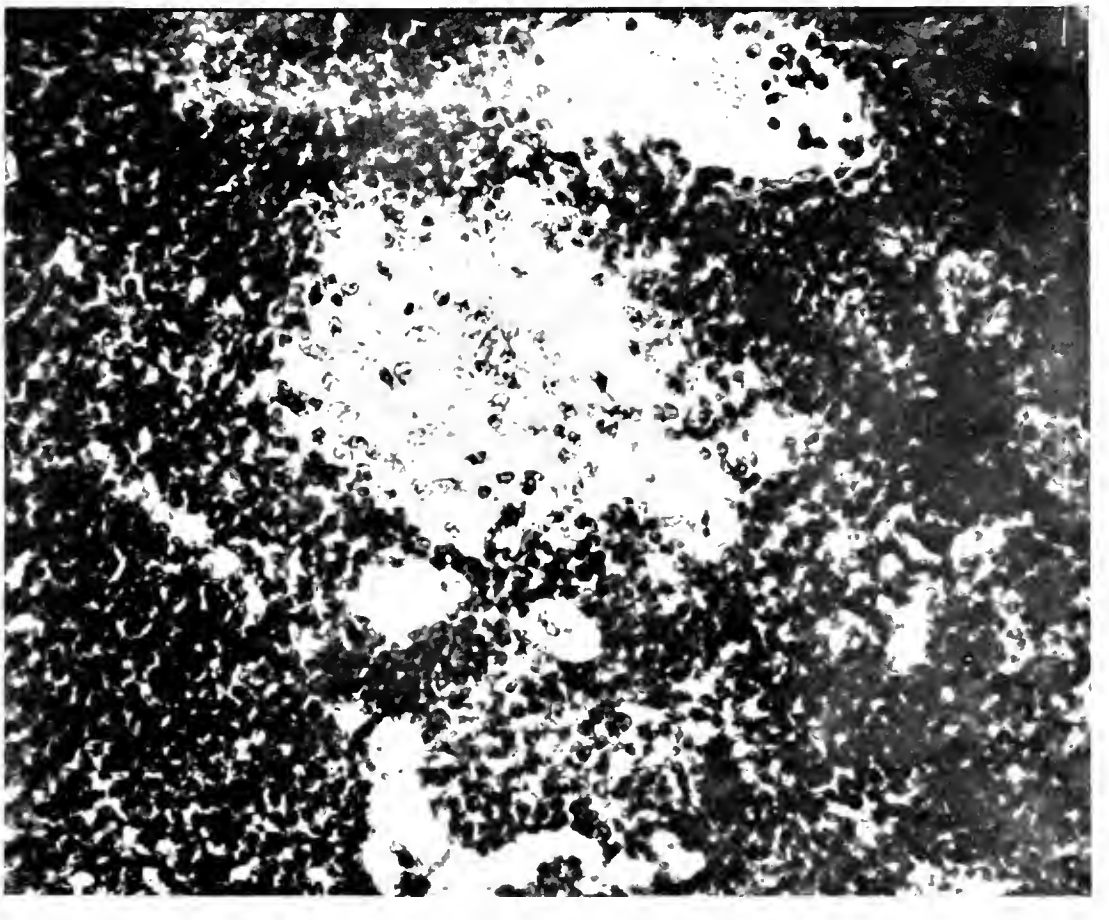


Fig. 4.—Primary miliary tubercle of mesenteric gland, undergoing hyaline transformation. Smaller hyaline droplets representing older healed lesions.

degeneration and necrosis found in the germ-centers and splenic follicles are usually repaired by *regeneration* of like tissue, and not by formation of scar-tissue. The same thing is true of the ordinary changes in the mesenteric nodes due to typhoid. Small focal necroses are repaired by regeneration; only in the case of larger areas of necrosis is there a definite mass of scar-tissue formed, and this does not often occur. Cases showing extreme necrosis of mesenteric nodes are probably usually fatal. A healed purulent focus will be replaced by a mass of scar-tissue, later becoming hyaline; but there is also a diffuse increase of stroma in the neighborhood, so that the picture differs from that of the ordinary hyaline droplet. Syphilitic changes in the lymph-nodes are also more diffuse and the stroma becomes hyaline. The small hyaline formations may, however, be found in lymph-nodes both in syphilis and in Hodgkin's disease. It becomes a question in such cases whether they are not the result of a coincident tuberculous infection.

The absence of hyaline formations in the tonsils, where infections are so common, the lack of positive proof showing their formation from focal lesions in typhoid, diphtheria, superficial burns, etc., and, on the other hand, the abundant proof that they are frequently formed from healed tubercles, must be regarded as very strong evidence in favor of my view that in the majority of, if not in all, cases they represent healed tuberculous lesions or tubercles. The relatively small number of hyaline formations in the mesenteric and bronchial nodes of non-tuberculous young people, while in tuberculous young people these glands usually show great numbers of hyaline droplets or masses, must be taken in support of the view of their tuberculous origin. The increasing number of the hyaline droplets with the advance of years supports our views as to the increasing opportunities for infection in adult and late adult life. My autopsy material contains but few children, hence I cannot speak positively as to the frequency of occurrence of hyalin in the mesenteric nodes of children, but the cases examined show a relative rarity of these formations in early life.

6. The formation of hyalin would seem to depend upon the slow healing and replacement by connective tissue following a slowly progressive tissue destruction. A focal tuberculous infection of low virulence supplies all the needed factors, and the slowly developing tubercle is finally mastered; the connective-tissue transformation takes place, and this new connective tissue still more slowly becomes converted into hyalin as it progressively contracts and becomes condensed.

The greater frequency of hyaline formations in the cervical, bronchial, and mesenteric nodes, is in itself suggestive of a tuberculous infection. At least, this is true of the cervical and bronchial nodes; in the case of the mesenteric nodes we shall be obliged to believe that the entrance of tubercle bacilli through the intestine is much more common than has been assumed. In

the case of pulmonary tuberculosis, the constant association, in the mesenteric nodes, of hyaline formations with miliary tubercles, and the presence of all possible stages between these two, proves beyond all doubt that such hyaline formations can be the result of healing tubercles. Further, in a number of cases, much greater than we have supposed, miliary tubercles, in stages of healing and hyaline transformation, are found in the mesenteric nodes when no active tuberculosis is found elsewhere in the body.

In the presence of pulmonary disease, the mesenteric tubercles may be easily explained as the result of bacilli gaining entrance to the intestine through ingested sputum. When pulmonary disease is not present, and when no other tuberculous focus is present in the body, the entrance of the tubercle bacilli by way of the intestine must be the result of the presence of bacilli in dust swallowed with the saliva, or of their presence in food. The latter alternative brings us to the disputed rôle of the bovine bacillus. In none of my cases was any attempt made to settle the character of the infection; inasmuch as the primary mesenteric tubercles were all discovered accidentally during the microscopical study of the lymph-nodes. Either human or bovine bacilli may be responsible for these lesions, what I wish to establish here is the view that the intestinal route is a *common* avenue of infection. If the small hyaline droplets in the lymph-nodes represent healed tuberculous lesions in the great majority of cases, then the constant presence of hyaline formations in the mesenteric nodes of adults must be interpreted as showing that *all adults receive tubercle bacilli through the intestine.* If we accept this, we have gone a long way toward accepting the enterogenous origin of pulmonary tuberculosis, for if tubercle bacilli so frequently gain entrance to the lymph-nodes, they just as frequently pass on through the thoracic duct to the lungs and to the bronchial glands. In the occurrence of hyaline formations in the mesenteric nodes, and the relationship existing between such hyalin and the healing of tubercles, the enterogenous theory of the origin of pulmonary tuberculosis finds strong support.

In conclusion this whole matter may be briefly summed up as follows:

1. Minute hyaline formations are present in the cervical, bronchial, and mesenteric nodes of all adults.

2. Such hyaline formations represent healed chronic miliary lesions.

3. Such lesions are, in the great majority of cases, if not in all, miliary tubercles.

4. The intestinal entrance of tubercle bacilli must be a very frequent occurrence.

5. Pulmonary tuberculosis may be caused in a large number of cases by bacilli taken into the upper air-passages in dust, swallowed with the saliva, passed through the intestinal wall into the thoracic duct, and thence carried to the lungs.

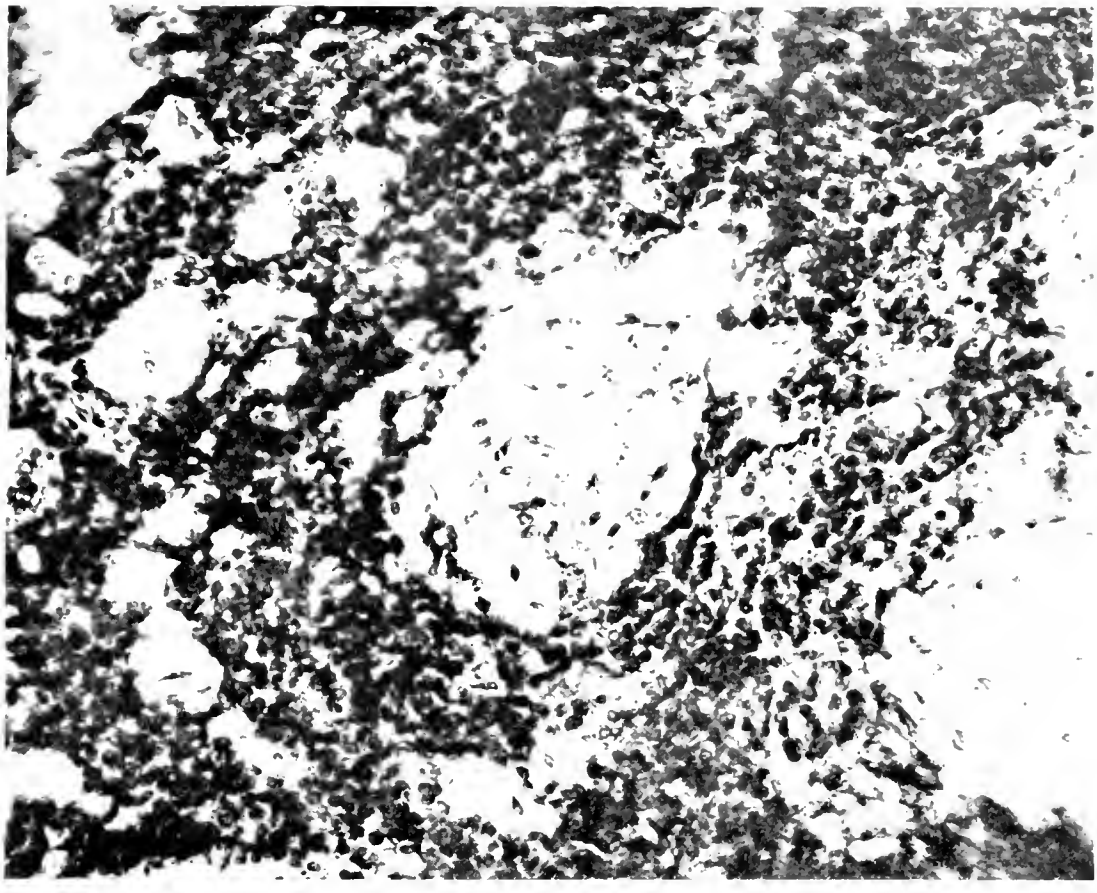


Fig. 5.—Various stages of hyaline transformation of miliary tubercles of mesenteric gland.

Fig. 6.—Characteristic hyaline droplets found constantly in mesenteric glands of adults. According to author's view they represent healed lesions—tubercles.

UEBER HISTOGENESE DES KNOCHENTUBERKELS.

Von Dr. Joseph Kertesz,
Budapest.

Zur Klärung der Anfangsstadien der Knochenmarkstuberkulose stellte Autor im pathologischen Institut des Herrn Hofrat Prof. Dr. Pertik Untersuchungen an.

Er injicierte eine Tuberkelbazillen enthaltende Emulsion (physiologischer Kochsalzlösung) in das Knochenmark des Femur der Versuchstiere (Kaninchen), und erhielt durch Tötung derselben innerhalb 1–8 Tagen ein Untersuchungsmaterial, welches die betreffenden verschiedenen Veränderungen des Knochenmarkes aufwies.

Nach seinen Untersuchungen beschreibt er die Histogenese der tuberkulösen Osteomyelitis folgendermassen:

Die in das Knochenmark gelangten Tuberkelbazillen werden sehr schnell durch polymorphe Leukocyten umringt, welche sammt einem Teile der im Invasionsbezirke sich befindenden fixen Bindegewebszellen binnen 2–3. Tagen zu Grunde gehen. Ein anderer Teil dieser fixen Bindegewebszellen, sowie die desquamierten Endothelzellen der Kapillaren, vermehren sich amitotisch.

Diese Zellen, sowie die jungen proliferierten Elemente, gruppieren sich um den Tuberkelbazillus und bilden den epithelioiden Tuberkel, welcher am 4. Tage schon vollkommen ausgebildet ist. Die ersten Tuberkel-Riesenzellen sah Autor am 5. Tage auftreten, welche in diesem Stadium durch Confluieren der vermehrten Kapillarendothelien entstehen. Am 7. Tage treten Lymphocyten um den Tuberkel herum auf, welch' letzterer in seiner Mitte schon Zeichen einer Verkäsung aufweist. Am 8. Tage dringen die Lymphocyten in den Tuberkel hinein und es entsteht der lymphoide Tuberkel.

Die anfängliche Leukocytenanhäufung entsteht zweifellos durch chemotaktische Wirkung der Bazillen. Die Leukocyten gelangen jedoch nicht aus den Blutgefässen in die Nachbarschaft der Bazillen, sondern aus den Septen des angrenzenden Knochenmarkes. Die sogenannten wandungslosen Bluträume des Knochenmarkes füllen sich nach Auswanderung der Leukocyten mit roten Blutkörperchen. Diese Bluträume haben nach den Beobachtungen des Autors eine homogene, stellenweise dicke Wandung. Den endothelialen Ueberzug der Wandungen, welchen Langemann beschreibt, sah Autor nicht.

Die Lumina der Kapillaren in der Umgebung des tuberkulösen Gewebes werden entweder durch Druck obliteriert oder sie verschwinden dadurch, dass

das Endothel desquamiert und sich vermehrt. Die Adventitia grösserer Gefässe zeigt auch Zeichen einer regen Proliferation. Die Riesenzellen können nach der Auffassung des Autors auf verschiedene Weise zustande kommen.

Die Anhäufung und Einwanderung der Lymphocyten um und in den Tuberkel am 7. beziehungsweise 8. Tage geschieht ebenfalls aus dem benachbarten Knochenmarks gewebe, wodurch dieses, den Tuberkel umgebende Gewebe an lymphoiden Zellen ärmer wird. Die bindegewebigen Elemente sind indessen in diesem Gewebe vermehrt. Es ist sehr wahrsheinlich, dass diese Vermehrung des Bindegewebes die Obliteration der Bluträume verursacht, an deren Stellen man reticuläres Bindegewebe antrifft. So bewirkt, abgesehen von den Toxinen der Bazillen, die Obliteration der Kapillaren und der Bluträume in der Umgebung des Tuberkels den Zerfall, die Coagulations-Nekrose desselben.

The Histogenesis of Tuberculosis of Bones.—(KERTESZ.)

The tubercle bacilli introduced into the bone-marrow of rabbits are quickly surrounded by polymorphous leukocytes, and they, as well as some of the fixed connective-tissue cells situated in the invaded district, are destroyed within two or three days. Other fixed connective-tissue cells, as well as the desquamated endothelial cells of the capillaries, increase amitotically. These cells, as well as the young proliferated elements, group themselves about the tubercle bacilli and form the epithelioidal tubercle, which is completely formed as early as the fourth day. The first tuberculous giant-cells appeared on the fifth day, originating through a confluence of the augmented endothelium of the capillaries. On the seventh day lymphocytes group about the tubercle, which shows signs of caseation in its center. On the eighth day the lymphocytes penetrate the tubercle; thus originates the lymphoid tubercle. The leukocytes reach the neighborhood of the bacilli from the septa of the neighboring bone-marrow.

The lumina of the capillaries in the neighborhood of the tuberculous tissue are obliterated, through pressure or through the desquamation of the endothelium. The giant-cells are formed in different ways.

The accumulation and the migration take place also from the neighboring bone-marrow. The connective-tissue elements of this tissue proliferate, obliterating the blood-spaces.

The destruction of the tubercle, its coagulation necrosis, is caused by the obliteration of the capillaries and the blood-spaces in its neighborhood.

THE KIDNEYS IN CASES OF TUBERCULOSIS OF THE LUNGS.

By Dr. Joseph Walsh,
Philadelphia.

The kidneys in cases of tuberculosis of the lungs present principally the changes that would be expected in a chronic infectious disease, namely, first, those specific to the general disease, like tubercles and amyloid, and, second, the general inflammatory or degenerative changes common to many infectious diseases. In previous* studies I have dwelt especially on tubercle bacilli in the urine, tubercles in the kidneys, the common inflammatory conditions observed, and the relation of chronic focal interstitial nephritis to tuberculosis. The present paper is a short résumé of the former work, which has been somewhat extended, with some special remarks on chronic general interstitial nephritis.

Tubercles.

In the 106 pairs of kidneys studied especially for tubercles, each kidney being cut into about 70 macroscopical sections, tubercles were found 57 times (53.8 per cent.). On account of the frequency of round-cell infiltration in the kidneys of these cases, only absolutely typical tubercles, showing caseation and giant-cells, were counted. This number, therefore, represents the minimum, since it will be readily granted that many tubercles, especially young ones, show neither caseation nor giant-cells. In 52 cases in which the location was recorded, these tubercles were found in the cortex 26 times; in both cortex and pyramids, 24 times; and in the pyramids alone, twice. They were usually in small numbers (one to five), and appeared as if they had developed in the last days of the disease. Altogether, there were twelve cases showing numerous tubercles—in other words, a condition of miliary tuberculosis.

Tubercles were found in association with all the different forms of nephritis in such numbers that the tubercles could be considered to have little or

* Proceedings of the Philadelphia Pathological Society, vol. vi, No. 6, 1903; the Second and Third Annual Reports of the Henry Phipps Institute; Transactions of the International Congress on Tuberculosis held in Paris in 1905; and the Transactions of the Second Annual Meeting of the National Association for the Study and Prevention of Tuberculosis.

no influence on the nephritis and, reversely, the nephritis little or no influence on the development of the tubercles. Of the 44 cases of acute parenchymatous nephritis, 21 showed tubercles; of the 36 cases of chronic parenchymatous nephritis, 22 showed tubercles; of the 2 cases of diffuse nephritis, 1 showed tubercles; of the 12 cases of chronic general interstitial nephritis, 7 showed tubercles; and of the 12 cases of cloudy swelling, 6 showed tubercles.

There were three cases of ulcerative tuberculosis—two of the left and one of the right kidney. These were typical cases and require no comment.

The urine of a certain number of these cases was examined for tubercle bacilli. In addition, under the direction of Dr. Ravenel and myself, Mr. Smith made an inoculation study of 21 urines. He inoculated each time the carefully washed sediment of about 2000 c.c. of urine. Altogether, 54 guinea-pigs were used. Out of the 21 cases, 4 sets of guinea-pigs died of septicemia in three or four days. Out of the remaining 17, tubercles were found in the guinea-pigs after six weeks 14 times (82.5 per cent.).

The following table shows the details of this inoculation study in 12 patients who have since died in the hospital. One out of the 12 urines showed tubercle bacilli to staining (that is, to microscopical examination), and tubercles were found in the kidneys of the patient, but the urine caused septicemia in guinea-pigs every time injected. One of the urines showed no tubercle bacilli on staining, did not produce tuberculosis in the guinea-pig, and the kidneys of the patient showed no tubercles. One of the urines, showing no tubercle bacilli on staining, produced tuberculosis in the guinea-pig, yet the kidneys of the patient showed no tubercles. Out of the remaining 8 urines, all showed tubercle bacilli on staining, 7 urines produced tuberculosis in the guinea-pig, and 5 times the kidneys of the patients showed tubercles. One urine showed tubercle bacilli on staining, and the kidneys of the patient showed tubercles without the urine having any effect on guinea-pigs. Three urines showed tubercle bacilli on staining, and the guinea-pigs injected showed tuberculosis without tubercles being found in the kidneys of the patients.

In other words, it would seem that the kidneys may contain tubercles, bacilli be excreted and found in the urine, and yet the urine be incapable of infecting guinea-pigs (one case), and, again, that living tubercle bacilli capable of infecting guinea-pigs may pass through the kidneys without the kidneys showing tubercles (three cases). It is to be remembered that these kidneys were cut into pieces $\frac{1}{20}$ to $\frac{1}{10}$ inch in diameter, and every abnormality, no matter how slight, was mounted and stained. The tubercle bacilli found in the urine in these cases were found after centrifugating 2000 c.c. of urine, and sometimes not then on the first examination, but only on the second or even third examination.

Case No.	Age.	Sex.	Married, Single.	Entered Hospital.	Died.	Duration of Illness in Years.	Edema.	Tubercle Bacilli in Sputum.	Urine Examination.	Tubercle Bacilli in Urine.	Number of Pigs Injected.	Sediment of Urine Injected.	Pigs that Died of Septicemia.	Tuberculosis in Pigs.	Diagnosis of Kidney Condition in the Patient.
73	38	F.	M.	2-1-'05	2-20-'05	23	No.	+	Acid 1014, albumin present.	+	2	1200 c.c.	0	+	Chronic parenchymatous nephritis with chronic focal interstitial nephritis. Tubercles.
106	27	M.	S.	1-20-'04	11-20-'05	4	No.	+	Acid 1022, albumin absent.	0	4	3400 c.c.	+ two	+ two	Mild grade of acute parenchymatous nephritis with chronic focal interstitial nephritis. Tubercles.
2481	38	M.	M.	2-1-'05	3-6-'05	15	No.	+	Acid 1010, albumin present, no casts.	+	2	2000 c.c.	0	+	Ulcerative tuberculosis of right kidney, chronic general interstitial nephritis of left kidney. Tubercles.
2676	40	M.	M.	2-1-'05	4-27-'05	2	No.	+	Acid 1028, albumin present.	+	2	900 c.c.	0	0	Amyloid degeneration, chronic parenchymatous with chronic focal interstitial nephritis. Tubercles.
2977	28	F.	M.	3-4-'05	6-25-'05	½	Marked of both feet.	+	Acid 1026, albumin absent, hyaline and waxy casts.	+	2	3000 c.c.	+ one	+ one	Acute parenchymatous nephritis with chronic focal interstitial nephritis. No tubercles.
2989	47	M.	S.	12-16-'04	1-30-'05	20	No.	+	Acid 1026, albumin present, few granular and epithelial casts.	+	2	1200 c.c.	0	+	Cloudy swelling with chronic focal interstitial nephritis. Tubercles.
3207	45	F.	M.	5-30-'05	6-24-'05	3	No.	+	Acid 1014, albumin present.	0	2	400 c.c.	+ one	+ one	Acute parenchymatous nephritis with chronic focal interstitial nephritis. No tubercles.
3355	28	F.	S.	5-18-'05	8-4-'05	3	No.	+	Acid 1016, albumin present, no casts.	+	2	1400 c.c.	+ one	+ one	Mild grade acute parenchymatous nephritis. No tubercles.
3388	36	M.	M.	5-29-'05	6-4-'05	½	No.	+	Acid 1020, albumin present, a few finely granular casts.	+	2	2700 c.c.	0	+	Chronic parenchymatous nephritis with chronic focal interstitial nephritis. No tubercles.
3432	20	F.	S.	6-21-'05	8-19-'05	3	No.	+	Acid 1020, albumin absent, casts present.	+	4	2000 c.c.	+ four	0	Cloudy swelling with chronic focal interstitial nephritis. Tubercles.
3440	26	M.	S.	6-14-'05	8-11-'05	1½	No.	+	Acid 1022, albumin present, few granular and waxy casts.	0	3	5000 c.c.	+ one	0	Chronic parenchymatous nephritis. No tubercles.
3697	37	F.	S.	12-26-'05	1-10-'06	1	No.	+	Acid 1020, albumin absent.	+	4	6000 c.c.	+ three	+ one	Chronic parenchymatous nephritis with slight chronic focal interstitial nephritis. Tubercles.

Amyloid.

In the 106 cases studied for amyloid, it was found only 7 times (6.6 per cent.). This constitutes all the amyloid found both macroscopically, by means of the test with Lugol's solution, and microscopically, by means of gentian-violet.

Of the 7 cases, 3 responded to both the Lugol's and gentian-violet test, and of these, 1 (No. 1577) showed amyloid also in the spleen and 2 (Nos. 3548 and 5014), in both the spleen and liver. The remaining 4 (Nos. 236, 714, 1032, and 2102) responded neither to Lugol's nor the gentian-violet test. In all 4, however, the spleen was amyloid, and in 1 (No. 2102) also the liver and the kidneys showed a sufficient number of hyaline glomeruli to make a diagnosis of beginning amyloid. In this series of 106 cases, amyloid was found in the spleen 8 times (17 per cent.), in the liver 8 times (8 per cent.), and in the intestines once (0.94 per cent.). It was never found in the kidneys exclusively.

In the 106 cases studied especially for the general conditions the following were found:

Cloudy swelling	12
Mild grade acute parenchymatous nephritis	27
Acute parenchymatous nephritis	16
Marked acute parenchymatous nephritis	1
Acute diffuse nephritis	2
Mild grade chronic parenchymatous nephritis	8
Chronic parenchymatous nephritis	24
Marked chronic parenchymatous nephritis	4
Chronic general interstitial nephritis	12
Slight chronic focal interstitial nephritis	38
Chronic focal interstitial nephritis	30
Marked chronic focal interstitial nephritis	11

The terms practically explain themselves. The mild grade acute parenchymatous nephritis was scarcely more than cloudy swelling; acute parenchymatous nephritis signifies a definite degenerative condition, but one not capable, for instance, of causing death; the marked acute parenchymatous nephritis was of sufficient degree to possibly cause death. Similar distinctions hold in regard to the chronic parenchymatous conditions; the mild grade chronic parenchymatous nephritis was but little removed from the normal; the chronic parenchymatous nephritis was a definite condition, and the marked grade might have been the cause of death. The slight chronic focal interstitial nephritis consisted of one to three or four small focal interstitial areas, frequently located immediately under the investment; the chronic focal consisted of a number of areas, both beneath the investment and scattered through the cortex, and the marked chronic focal consisted of so many areas that a diagnosis of chronic general interstitial nephritis might be made unless a number of sections were studied.

Only two of the eleven cases in which a marked condition of focal interstitial nephritis is described were described also as chronic general interstitial nephritis, that is, the condition was a chronic general interstitial nephritis with focal areas, in which the thickening of the interstitial tissue was very marked; the remaining nine were in association with acute and chronic parenchymatous nephritis. Eight of these nine appeared to be gradually developing into what could only be described as a chronic general interstitial nephritis, and furnish the basis of one of the varieties of chronic general interstitial nephritis, which is dealt with later.

There were twelve cases of chronic general interstitial nephritis, none of them marked conditions. One (Case No. 3896) was a definite subcapsular interstitial nephritis, the thickening of the interstitial tissue being limited to the outer half of the cortex. In one (Case No. 2957) the thickening of the interstitial tissue was not absolutely general, and there was question whether it ought to be named a marked chronic focal interstitial or a chronic general interstitial nephritis. The remaining ten were ordinary cases of not marked chronic general interstitial nephritis.

Special Remarks in Relation to Interstitial Nephritis.

In 106 kidneys from cases of tuberculosis there were 10 pure cases of chronic general interstitial nephritis. In the 44 kidneys studied from other chronic diseases there were 23 cases of chronic general interstitial nephritis. Moreover, the chronic general interstitial nephritis in this latter category was much more marked than in the former. This study of the kidney leads to the conclusion that tuberculosis of the lungs is antagonistic* to the ordinary chronic general interstitial nephritis, just as it appears antagonistic to chronic general sclerosis of other organs or tissues. It appears, however, to rather favor the development of local sclerosis. I have endeavored to learn the pathogenesis of the focal interstitial nephritis so frequently met with, but so far unsuccessfully.

The study of what might be called early cases of chronic general interstitial nephritis in tuberculosis, and the comparison of them with the advanced cases of chronic general interstitial nephritis, appeared to show the following different kinds of chronic general interstitial nephritis which I believe are due to different causes, namely:

1. Chronic general interstitial nephritis, beginning generally, and secondary to, a chronic parenchymatous nephritis (secondary interstitial nephritis).

2. Chronic general interstitial nephritis, beginning between the tubules and not dependent on a preceding parenchymatous condition (true or primary chronic general interstitial nephritis). This is the common form of chronic

*The comparison as to the age, occupation, etc., of the tuberculous cases and non-tuberculous has already been carried out in the Third Annual Report of the Henry Phipps Institute.

general interstitial nephritis, and the majority of our cases, both tuberculous and non-tuberculous, appeared to correspond to it.

3. Chronic general interstitial nephritis, beginning in or about the Malpighian bodies. I have never seen a case of fully developed chronic general interstitial nephritis in which I could be sure this was the mode of origin, yet I have seen suggestions which warrant me in thinking that such a variety of chronic general interstitial nephritis occurs. These suggestions were in cases of chronic focal interstitial nephritis in which the focal thickening was limited to the tissue around the Malpighian bodies. Whether or not the cases of chronic general interstitial nephritis, in which the Malpighian bodies are practically all fibroid, bear any relation to this form of nephritis I do not know. Every one has remarked cases, however, in which the Malpighian bodies were little or not at all affected, and again cases in which the fibroid condition of the Malpighian bodies was the most striking feature. This does not imply that all cases with marked fibroid Malpighian bodies must have begun in the Malpighian bodies, because I have no doubt that these bodies are sometimes affected secondarily.

4. Chronic general interstitial nephritis developing from a chronic focal interstitial nephritis, that is, due to the gradual approximation of a large number of chronic focal interstitial areas. Unlike the condition in the second and third varieties, these focal interstitial areas are not particularly localized either about the tubules or Malpighian bodies, but are generally scattered. This form is undoubtedly frequent, yet, as far as I know, has not been described. Eight cases out of the 106 showed a chronic focal interstitial nephritis which, I believe, in time, could only be described as chronic general interstitial nephritis.

Chronic general interstitial nephritis, spreading from the larger blood-vessels (arteriosclerotic interstitial nephritis), is usually a focal interstitial nephritis, beginning about the blood-vessels between the cortex and medulla, and gradually spreading through the former, and only sometimes shows an absolutely general dissemination. It is commonly thought that all chronic general interstitial nephritides show a thickening of the blood-vessels. This is not true. Out of 12 cases of chronic general interstitial nephritis in connection with tuberculosis of the lungs, only 5 (42 per cent.) showed thickening of the blood-vessels. Moreover, the reverse is also seen, for out of 92 recorded cases of other conditions, like acute and chronic parenchymatous nephritis, 32 showed thickening of the blood-vessels (34.8 per cent.), though frequently the thickening was very slight. This form of nephritis was found in 2 out of 44 kidneys from non-tuberculous, but in none of the kidneys from tuberculous.

Chronic general interstitial nephritis due to passive congestion (cyanotic

induration) begins in the center of the cortex, about the small venules. This form of nephritis was found in none of the kidneys in this study.

Capsular interstitial nephritis, a condition beginning at the capsule, occurred once among the kidneys from cases of tuberculosis.

Los Riñones en los Casos de Tuberculosis de los Pulmones.—(WALSH.)

Los riñones en los casos de tuberculosis de los pulmones, mostraon tuberculosis ulcerativa en 2.8 per cent., tuberculosis positiva en 53.8 per cent., degeneración amiloidea en 6.8 per cent., infiltración en 11.3 per cent., nefrítis parenquimatosa aguda en 41.5 per cent., nefrítis difundida en 1.9 per cent., nefrítis parenquimatosa crónica en 33.9 per cent., nefrítis intersticial crónica y generalizada en 11.3 per cent. y nefrítis intersticial crónica focal en 74.5 per cent.

Esto parece que la nefritis intersticial crónica localizada puede depender de la tuberculosis, ó de sus infecciones mistas, mas la patogenesis no se sabe todavía.

Las condiciones crónicas intersticiales generalizadas fueron pocas en número y de caracter leve, por lo tanto es posible la existencia de un antagonismo entre la tuberculosis y la nefritis intersticial crónica generalizada.

Inoculación de de la orina en los cobayos demostró la presencia del bacilo de la tuberculosis en la orina en 82.5 per cent. de los casos experimentados.

Les reins dans les cas de tuberculose des poumons.—(WALSH.)

Les reins dans les cas de tuberculose des poumons révèlent la tuberculose ulcérative dans 2.8 per cent. des cas, des tubercules positifs dans 53.8 per cent., la dégénerescence amyloïde dans 6.6 per cent., tuméfaction fébrile des cellules du parenchyme dans 11.3 per cent., néphrite parenchymateuse aigue dans 41.5 per cent., néphrite diffuse dans 1.1 per cent., néphrite parenchymateuse chronique dans 33.9 per cent., néphrite interstitielle générale chronique dans 11.3 per cent. et néphrite interstitielle focale chronique dans 74.5 per cent.

Il paraît possible que la néphrite interstitielle focale chronique peut être determinée par la tuberculose ou les infections mixtes qui la compliquent; mais la pathogénie n'est pas encore connue.

Les néphrites interstitielles chroniques générales étaient peu nombreuses et d'un caractère léger; donc il-y-a peut-être un antagonisme entre la tuberculose et la néphrite chronique générale interstitielle.

L'inoculation des urines des malades dans les cobayes révélait des bacilles tuberculeux dans les urines de 82.5 per cent. des cas.

Die Nieren in Fällen von Lungen-Tuberkulose.—(Walsh.)

Die Nieren in Fällen von Lungen-Tuberkulose zeigten ulcerative Tuberkulose in 2.8 per cent., positive Tuberkeln in 53.8 per cent., amyloide Degeneration in 6.6 per cent., trübe Schwellung in 11.3 per cent., akute parenchymatöse Nephritis in 41.5 per cent., diffuse Nephritis in 1.9 per cent., chronische parenchymatöse Nephritis in 33.9 per cent., chronische allgemeine interstitielle Nephritis in 11.3 per cent., und chronische fokale interstitielle Nephritis in 74.5 per cent.

Es erscheint als möglich, dass die chronische fokale interstitielle Nephritis, oder ihre Mischinfektion, von der Tuberkulose abhängen mag, aber die Pathogenese hat man noch nicht kennen gelernt. Die chronischen allgemeinen interstitiellen Bedingungen waren wenige an Zahl und milden Grades; daher ist ein Antagonismus möglich zwischen Tuberkulose und chronischer allgemeiner interstitieller Nephritis.

Die Inokulation des Urins in Meerschweinchen zeigte in 82.5 per cent. der Fälle Tuberkelbazillen im Urin.

PERIOSTITIS ET ADIPOSITIS MULTIPLEX TUBERCULOSA TOXICA TREATED WITH MARMOREK SERUM.

By O. Amrein, M.D.,

Arosa, Switzerland.

Two years ago a patient came under my care at Arosa who showed an unusual and interesting type of tuberculous disease which I could not find described anywhere in our literature.

The anamnestic data are the following: The patient (female) was thirty-two years old. She had been well and strong as a child, and was working as a teacher in perfect health until 1899. In that year, for some six months, she nursed her sister, who subsequently died of tuberculosis of the lungs. Very soon afterward a general weakness and lassitude became more and more perceptible, and after some months pains appeared in the legs, in the loins, and in the sacral part of the vertebral column, at first dull, then more and more localized and definite, and eventually down the tibia along the bone itself and around the joints of the feet. Then she was treated with massage and electric baths, but became worse. She still, however, continued her work at school. Notwithstanding the treatment, pains around the knee-joints, especially on the left side, were added to the pains and swellings in the legs, and afterward in the arms, where big swellings over the shoulders and down along the sides of the upper arms developed. These next appeared around the hips, and later on in the neck.

In 1906 the patient came to Arosa; her condition was then as follows: There was a swelling on the neck (seventh to ninth vertebra), such as is found in spondylitis, and a granular roughness which was very painful to the touch, along and over the left jaw-bone. There were diffuse swellings over the shoulders and over the deltoid muscles, but the skin was not thickened, and the muscles themselves were unaffected, although the subcutaneous fat-tissue showed circumscribed and hard swellings, which were also very painful to the touch. Similar swellings existed over the hips (gluteus maximus) and along the upper parts of the thighs. Along the crista tibiæ, on both sides, were rough granules. Over the muscles of the lower part of the thighs

were to be seen diffuse swellings of such extent that the legs had all the appearance of elephantiasis.

The greatest sensibility to touch was over the sacral region of the backbone, with diffuse swellings in the neighborhood. There was also granular roughness over the ninth rib on the right side, and over the sternum.

Everywhere the skin itself was unaffected and could be felt unthickened. It could be lifted up in the usual way, even where there were diffuse swellings. There was a thickening of the adipose tissue beyond the affected periosteum of the jaw-bone, of the ninth rib, of the cristæ tibiæ, and of the sternum, but the bones themselves were not affected. Besides the spondylitis cervicalis and sacralis there were, therefore, to be diagnosed a periostitis and adipositis multiplex.

As regards other symptoms, the top of the left lung showed a slight lesion, but no glandular swellings were to be found. The temperature was 37.4° to 37.6° C. in the mornings and evenings, and 37.8° to 38° C. late in the afternoon.

What was the cause of this disease? Such swellings, I am told, are sometimes found in gouty people. Luetic patients may show similar ones also. But both conditions were to be excluded in this case. The affection of the left apex, slight as it was, inevitably pointed to tuberculosis.

This diagnosis was justified by experimental injections of tuberculin, on the administration of which a reaction of the temperature to 37° C. and more, and a reaction in loco, that is, increased pains and increased swellings, took place. Neither any eruption nor abscess formation ever was to be seen; the skin never became red or inflamed, and the swellings remained hard, like infiltrations. It is to be supposed that they were caused, as well as the periostitis, by the tuberculotoxins, and I therefore call the whole affection periostitis et adipositis multiplex tuberculosa toxica.

I kept this patient in bed for six and a half months and treated her with compresses and bandages of absolute alcohol, combined with the exhibition of iodipin. Tuberculin treatment, even with the smallest doses of tuberculin Denys and tuberculin Béraneck, was impossible, as the pains became unbearable after the injections. The swellings began to diminish after some months, and the patient, who had been absolutely unable to sit or to walk, but was obliged to lie prone on her back all the time, could begin to walk and move about a little.

On account of her mother's death she had to leave Arosa in the spring of 1907, but she came back again in the following winter, and then showed renewed and increased swellings and pains, but only in the same places as before.

I made a trial of Marmorek serum, and was astonished to see the influence

it exercised upon the affected parts. After the applications of the serum, which was given as an enema every morning for a week, with intervals of two or three weeks, increased pains appeared and the swellings became hot, but the temperature, which had previously gone up to 37.4° to 37.6° C. in the evening, became normal. After the first week the patient could move about better and bend herself, while the second series of enemata brought about a still more distinct improvement. The contours of the foot-joints, knees, etc., became more and more visible, and the elephantiasic appearance of the legs disappeared altogether. The patient still continues with the serum treatment, interrupting it for two or three weeks between each series of enemata. She is happy and full of life again, is becoming more and more a normal member of human society, and is given back to life after years of pain and suffering.

ZUR PATHOLOGIE DER PERITONEALTUBERKULOSE.

Von Dr. med. Walter Altschul,
Prag.

Die Peritonealtuberkulose ist ein Lieblingskind der chirurgischen Literatur, aber ein Stiefkind der pathologischen Anatomen. In der ganzen pathologisch-anatomischen Literatur der letzten Jahre habe ich nicht viel über die Aetiologie derselben gefunden. Und doch ist sie kein so seltener Befund bei den Sektionen; unter 10,322 Protokollen, die ich im deutschen pathologischen Institut in Prag daraufhin nachgesehen habe, fand ich 299 Fälle sicherer Peritonealtuberkulose. Man war früher der Ansicht dass alle Peritonealtuberkulosen entweder vom weiblichen Genitale oder vom Darm ausgehen.

Das weibliche Genitale ist als Infektionsquelle gewiss nicht in allen Fällen auszuschalten, und nach dem Sektionsmaterial, das mir zur Verfügung steht, glaube ich, ist die Annahme berechtigt, dass eine Fortleitung zumindest möglich ist. Allerdings muss man in Betracht ziehen, dass einerseits die Infektion des Peritoneums und des Genitales gleichzeitig und unabhängig von einander zustandekommen, andererseits aber das Genitale auch vom Peritoneum aus infiziert werden kann. Für die letztere Eventualität sprechen die Fälle von Tuberkulose des abdominellen Tubenendes oder solche Fälle wobei rezenter Uterustuberkulose das Fortschreiten der Infektion von der älteren Tubenaffektion zum Uterus zu ersichtlich ist. Überdies ist das prozentuale Verhältnis der weiblichen Personen gewiss nicht so überwiegend, dass man daraus auf ein grösseres Befallensein weiblicher Individuen schliessen dürfte; ich fand unter 299 Fällen von Peritonealtuberkulose 156 weibliche Personen—also, 52 Prozent; und von den letzteren war nur 52 mal Genitaltuberkulose zu konstatieren.

Die Tuberkulose des Darmes als alleiniger Ausgangspunkt der Peritonealtuberkulose anzunehmen, ist kaum zu verteidigen, da in einer grossen Anzahl von Fällen gar keine Darmaffektion gefunden wird.

So scheint es denn notwendig andere Infektionsquellen für das Peritoneum zu suchen, und da muss man wohl zuerst an die peribronchialen Lymphdrüsen denken, die bekanntlich der häufigste und in einer grossen Anzahl von Fällen der alleinige Sitz der Tuberkulose sind. Es drängt sich uns nun die Frage auf: Welches ist der Weg, den die Tuberkelbazillen aus der Brusthöhle in die Bauchhöhle einschlagen? Zwei Wege führen dahin: die Blutbahn und der Lymphweg.

Bei Benützung der Blutbahn müssten die Tuberkelbazillen zunächst in den Lungenkapillaren stecken bleiben, und daselbst Lungentuberkulose erzeugen. Nun gibt es aber Fälle von Tuberkulose des Peritoneums bei denen Lungentuberkulose vollständig fehlt (11 Fälle meiner Statistik). Gegen die Beteiligung der Blutbahn spricht auch der Umstand, dass bei miliarer Aussaat gewöhnlich das Peritoneum intakt bleibt. So kommt man also per exclusionem auf den Lymphweg.

Durch die Arbeiten von Sappey,* und in neuerer Zeit durch Küttner,† ist nachgeweisen dass eine Kommunikation zwischen Brust und Bauchhöhle durch Lymphgefässe tatsächlich besteht; Küttner hat sogar gefunden dass diese Gefässe für den Lymphstrom in beiden Richtungen durchgängig sind. Es ginge demnach der Infektionsweg von den peribronchialen Lymphdrüsen durch die perforierenden Lymphgefässe des Zwerchfells in die Bauchhöhle und zwar am häufigsten zu den retroperitonealen Drüsen, die fast jedesmal bei Peritonealtuberkulose miterkrankt sind. Dass dieser Weg auch wirklich eingeschlagen wird, beweisen Fälle, bei denen sich ausser in den peribronchialen Drüsen nur in den retroperitonealen Drüsen Tuberkulose vorfindet. Eine zweite Infektionsart ist der Durchtritt der Tuberkelbazillen durch das Zwerchfell und Lokalisation der Tuberkulose an der unteren Fläche desselben, wie sie in Initialfällen bisweilen vorkommt. Diese Anschauungen, die Tendeloo‡ in mehreren Aufsätzen vertreten hat, beginnen jetzt allgemein anerkannt zu werden.

Nun ist folgende Frage zu beantworten: Wann kommt es zu einer Tuberkulose der Lunge und wann zu einer Aussaat auf das Peritoneum? Woher kommt es, dass bei Peritonealtuberkulose die Lunge gewöhnlich wenig, manchmal überhaupt nicht affiziert ist? Tendeloo ist der Ansicht dass der Lymphstrom in der Richtung von der Brust- in die Bauchhöhle nur dann möglich ist, wenn der intrathorakale Druck grösser wird, und gibt als eine Ursache hierfür Verwachsungen der Lunge mit der Brustwand, besonders aber mit dem Zwerchfell an. In dem von mir durchgesehenen Material von mehr als 10,000 Sektionen waren bei den 299 Fällen von Peritoneal tuberkulosen 199 mal die Lungen adhärent (darunter in 26 Fällen nur eine Lunge), 54 mal fand sich nur eine Anwachsung an der Spitze. Von den restlichen Fällen (46) waren 33 mal die Lungen als frei angegeben; bei den übrigen 13 waren Verwachsungen nicht erwähnt, so dass man annehmen kann dass auch bei diesen Fällen die Lungen frei waren. Es ergibt sich also dass nur

* Sappey: Anatomie, Physiologie et Pathologie des Vaisseaux lymphatiques, Paris, 1874.

† Küttner: "Die perforierenden Lymphgefässe des Zwerchfells und ihre pathologische Bedeutung," Beiträge z. klin. Chirurgie, 1903, Bd. xl.

‡ Tendeloo: "Lymphogene retrograde Metastasen von Bakterien, Geschwulstzellen, und Staub aus der Brust- in die Bauchhöhle, besonders in para-aortalen Lymphdrüsen," Münchener med. Wochenschrift, 1904, No. 35. *Ibid.:* "Lymphogene retrograde Tuberkulose einiger Bauchorgane," Münchener med Wochenschrift, 1905, Nos. 21 und 22.

in ungefähr $\frac{2}{3}$ der Fälle stärkere Verwachsungen vorhanden waren, so dass die angeführte Ansicht Tendeloos wenigstens nicht für alle Fälle zutreffen dürfte. Ich habe sogar gefunden, dass gerade bei den sogenannten reinen Fällen von Peritoneal tuberkulose (d. h. bei Fällen wo nur noch Tuberkulose der bronchialen Drüsen vorhanden ist) die Lungen gewöhnlich nicht adhärent waren. Ich habe von diesem Gesichtspunkt aus 1023 Protokolle über Tuberkulosen untersucht und gefunden, dass bei 281 Fällen sich eine Tuberkulose der Bauchorgane fand; hiervon waren 190 mal die Lungen adhärent, d. i., in 67½%, 55 mal an der Spitze adhärent, d. i., in 19½%, und 36 mal frei, d. i., in 13%. Bei den 742 Fällen ohne Beteiligung der Bauchorgane waren adhärent 441, d. i., 59½%, an der Spitze adhärent 209, d. i., 28% und frei 92, d. i., 12½%. Der Prozentsatz der freien Lungen ist also bei Affektion der Bauchorgane sogar um ein geringes grösser als bei Fehlen derselben.

Durch die Ergebnisse dieser Untersuchung veranlasst, habe ich versucht eine andere Erklärung für die oben erwähnten Fragen zu finden, und habe mir folgende Ansicht zurechtgelegt:

Der Heilungsprozess der Tuberkulose in den Peribronchialdrüsen kann auf zweierlei Art vor sich gehen: vom proximalen, und vom distalen teile aus. Kommt es nun zu einer Propagation der Tuberkulose (was natürlich nicht immer der Fall sein muss), so ist dieser Unterschied von Bedeutung. Kommt es distal zu einer Ausheilung, so ist der Weg nur in den ductus thoracicus, *i. e.*, in die Blutbahn frei, und die Tuberkelbazillen gelangen in die Kapillaren der Lunge, wo sie stecken bleiben und Lungentuberkulose erzeugen. Beginnt die Ausheilung proximal, so ist der Weg in die Blutbahn verschlossen und es kommt nun zu einer retrograden Verschleppung durch die perforierenden Lymphgefässe des Zwerchfälls auf das Peritoneum. Natürlich kann bei Erkrankung mehrerer Bronchialdrüsen ein Teil proximal, ein Teil distal, ausheilen, und so wären dann jene Fälle verständlich, in denen bei schwerer Lungentuberkulose sich Peritonealtuberkulose vorfindet, wobei man keine der beiden als primär, sondern beide als sekundäre, Erkrankung von den peribronchialen Lymphdrüsen aus ansehen muss, wenn auch eine Affektion später auftritt als die andere.

Diese Ansicht, durch welche sich sämtliche Varietäten der Peritonealtuberkulose erklären liessen, will ich durchaus nicht als unbedingt feststehend hinstellen. Ich wollte nur eine Anregung geben in welcher Richtung, meines Erachtens, wir zu einer Erklärung der tuberkulösen Infektion der Bauchorgane gelangen könnten. Natürlich müsste diese Anschauung experimentell gestützt werden können; ich will versuchen, ob es mir gelingt, von den Peribronchialdrüsen aus nach Abbindung der zuführenden Lymphgefässe Injektionsmasse in die Blutbahn zu bringen, und umgekehrt nach Abbindung der abführenden Lymphgefässe die Bauchorgane zu injizieren, und werde seinerzeit darüber berichten.

The Pathology of Tuberculous Peritonitis.—(ALTSCHUL.)

Although tuberculous peritonitis is quite frequent, as indicated by the fact that the author found 299 cases among 10,322 autopsy reports, the recent pathological literature contains practically nothing about the etiology. It was formerly believed that all cases of tuberculous peritonitis originated in the female genitalia or in the intestine. Infection may be simultaneous and independent, in the female genitalia and in the peritoneum, or the genital infection may be secondary to that of the peritoneum, as shown by cases of tuberculosis of the abdominal end of the tube, and in cases of recent uterine tuberculosis in which it can be proved that the infection has reached the uterus from an old tubal focus. Although the percentage of cases is greater among females than among males, the difference is not sufficient to indicate a greater frequency among women. Among 299 cases of tuberculous peritonitis, the author found that 156, or 52 per cent., were women, and of these 156 cases only 52 showed tuberculosis of the genital organs. The intestine cannot be regarded as the sole point of origin of tuberculous peritonitis, as there are many cases without intestinal involvement. The peribronchial lymph-glands suggest themselves as the sources of the infection, which may spread either by the blood or by the lymph-channels. If the bacilli were carried by the blood, they would be arrested in the pulmonary capillaries and set up pulmonary tuberculosis; but there are many cases of tuberculous peritonitis without any pulmonary involvement (11 cases in the author's statistics). The fact that the peritoneum usually escapes in miliary tuberculosis is also against the blood paths. By exclusion we therefore arrive at the conclusion that the infection travels by way of the lymph-channels. Sappey and Küttner have shown a communication between the thoracic and abdominal cavities by way of the lymph-vessels, and Küttner found that the lymph passes in both directions through these vessels. The path of infection is, therefore, from the peribronchial lymph-glands through the perforating lymphatics of the diaphragm into the peritoneal cavity, chiefly to the retroperitoneal glands, which are almost always involved in tuberculous peritonitis. That the infection travels by this path is shown by those cases which only present tuberculous lesions in the retroperitoneal and peribronchial glands. The tubercle bacilli may also pass through the diaphragm, and produce localized tuberculosis of the lower surface of that membrane, as sometimes occurs in early cases (Tendeloo).

Under what conditions does pulmonary tuberculosis develop, and what are the factors which determine infection of the peritoneum? Why

are the lungs usually involved but little or not at all in tuberculous peritonitis?

Tendeloo is of the opinion that the lymph-stream can only travel from the thoracic cavity toward the peritoneal cavity when the intrathoracic pressure is greater, and he gives, as one of the reasons, the presence of adhesions binding the lung to the chest-wall, and particularly to the diaphragm. In the material which the author examined, and which amounted to more than 10,000 autopsies, 299 cases of tuberculous peritonitis showed pleural adhesions in 199 instances (adhesion of only one pleura in 26 cases); in 54 cases the adhesion was limited to the apex; in 33 of the remaining 45 cases the lungs were free, and in 13 adhesions were not mentioned, so that it may be admitted that the lungs were free in these cases also. It follows, therefore, that adhesions of any extent were present in only two-thirds of the cases; hence Tendeloo's theory does not apply to all cases. The author found, in the so-called cases of pure tuberculous peritonitis, that, in the cases in which only the bronchial glands were involved outside of the peritoneum, the lungs were usually not adherent. He studied 1023 autopsy reports of tubercular subjects with this point in view, and found that of the 281 cases which showed tuberculosis of the abdominal organs, 190, or 67½ per cent., had pleural adhesions; 55, or 19½ per cent., had apical adhesions; and 36, or 13 per cent., were free. In the 742 cases without involvement of the abdominal organs, 441, or 59½ per cent., had adhesions; 209, or 28 per cent., apical adhesions; and in 92, or 12½ per cent., the lungs were free. Hence the percentage of cases without pleural adhesions is slightly higher when the abdominal organs are involved than in cases without abdominal tuberculosis. The author suggests the following explanation: In tuberculosis of the peribronchial glands the healing process may begin in the proximal or in the distal portion. If the infection spreads, the manner in which the healing takes place is of some importance. If recovery begins in the distal portion, the bacilli can escape only into the thoracic duct, *i. e.*, into the circulation. The bacilli enter the capillaries of the lung, where they are arrested and produce a pulmonary tuberculosis. If healing begins in the proximal portion, access to the circulation is blocked, and the bacilli are carried in a retrograde direction through the perforating lymphatics of the diaphragm to the peritoneum. If several bronchial glands are affected, it is, of course, possible that healing may begin in the proximal end of some, and in the distal portion of others, which would explain those cases in which a severe pulmonary tuberculosis is associated with tuberculous peritonitis, and in which both processes are secondary to disease of the peribronchial lymph-glands, although one localization may appear later than the other.

THE LIVER IN TUBERCULOSIS.

By Dr. J. T. Ullom,
Philadelphia.

The liver in tuberculosis has been studied by a number of observers in the course of the last century. Among the earlier observers it was thought to be very rarely the seat of tubercles or other manifestations of the general disease, but with the improvement of microscopical and histological methods, we find that very few cases of tuberculosis go to autopsy without some evidence of hepatic disease.

Louis, in 1843, found tuberculosis of the liver but twice in 120 autopsies on tuberculous subjects. Forster, in 1854, was able, after prolonged search, to find but three cases of hepatic tuberculosis. In an investigation undertaken by Bristowe in 1858 to discover the relation between liver abscess and intestinal ulceration, he found that, of 167 cases of tuberculous ulcers of the intestines, but twelve cases showed "cavities in the liver." Waldenberg, in 1869, reports that it is the organ most frequently affected in experimental tuberculosis, but this is due to inoculation into the peritoneal cavity. Arnold, in 1880, considers it an almost constant finding in cases of tuberculosis. Simmonds, in 1888, found it in 76 per cent. in adults, 92 per cent. in children, and in 78 per cent. in general. Zehden, in 1897, found miliary tubercles in 50 per cent. of fatal cases, corresponding with the frequency of intestinal ulceration. Rolleston is inclined to put the average at less than 50 per cent. Rosenberger, in 1906, found miliary tubercles in 83.8 per cent. of livers examined histologically. White, in 1907, found them in 70.3 per cent.

Tuberculosis manifests itself in the liver as: (1) Miliary tubercles. (2) Solitary tubercles. (3) Tuberculous cirrhosis. We will examine them in order. Miliary tubercles are decidedly the most common manifestation of tuberculosis in the liver, and have been described by many observers. They are usually found in or adjoining the portal spaces, but may be found within the lobule. They are usually typical, and present the characteristic features of the miliary tubercle very beautifully on the background of liver substance.

Portal of Infection.—Infection of the liver may take place in utero, the bacilli being transmitted by the umbilical vein. Sabourin, in 1891, found miliary tubercles in the liver and spleen of a child eleven days old, in

whose mother there was phthisis pulmonalis, but no evidence of mammary or genital tuberculosis. He concluded that the infection traveled by way of the umbilical vein. Nocard, in 1895, reported a case of tuberculosis of the liver in a calf in whose mother's placental cotyledons there were tubercles containing giant-cells. Von Honl found tubercles in the liver and other organs of a fifteen-day-old child in whom the tubercle undoubtedly antedated birth. His reason for believing that they were older than fifteen days was the amount of fibrous tissue about the lesions. D'Arrigo inoculated female guinea-pigs with tuberculosis and then allowed them to become pregnant. Some went to term and others aborted. In those going to term, the offspring showed tubercles, particularly of the liver and the abdominal organs. In those aborting after the first half of pregnancy, there were tubercles and tubercle bacilli in the livers of the offspring. Bar and Renom inoculated into animals the blood from the cut umbilical cord of children born of tuberculous mothers. In two cases out of five the animals showed tuberculosis. In one case the child died, and portions of its organs were inoculated into animals and produced tuberculosis of the animals. From the observations of these authors we conclude that tuberculosis can be carried from mother to child by way of the umbilical vein, and that it manifests itself in the liver of the child.

In the adult the infection is generally considered to take place by way of the portal vein. Rolleston thinks that the infection takes place via this vein in chronic tuberculosis coming from ulcers in the intestine, and in acute tuberculosis by way of the hepatic artery. This view is also held by Zehden, who thinks that the initial foci are likely to be in the intermediate zone of the lobule, where the lumen of the vessels is the narrowest. Orth thinks that the infection travels from the portal vein by way of the lymph-channels. Kotlar made very careful examinations of the liver, both histologically and bacteriologically, and came to the conclusion that the infection was hematogenous, and not via the bile-ducts. Lancereaux thinks that the infection comes from the intestine by way of the portal vein. Klebs thinks, with Zehden, that the infection starts in the intermediate zone and spreads peripherally by way of the lymph-channels. Gibbert and Lion produced tuberculosis of the liver by the injection of tubercle bacilli into the portal vein. The tubercles were found partially in the portal spaces and partially in the acini.

We submit the results of the histological examination of 100 livers. The blocks were cut as for routine histological work, no especial care being taken to pick out pieces of tissue that seemed to contain tubercles. Of the 100 livers, 79 were found to contain miliary tubercles. Some of these lacked the giant-cells, but other characteristics were present, and we had no hesitancy in calling them tubercles.

Seventy-four livers were stained for tubercle bacilli, with a positive result in 28, a percentage of 37.9. The infrequency with which tubercle bacilli are found in the liver has been commented upon by a number of observers, and we found that they were extremely hard to demonstrate. In 2 cases of acute miliary tuberculosis we found them in large numbers, but in all the rest we could find only a few after a prolonged search.

The position of the tubercles was periportal, 40 times; intra-acinal, 17 times, and both periportal and intra-acinal, 22 times. In a series of 45 cases of miliary tuberculosis of the liver examined especially with regard to intestinal ulceration this complication was found 38 times. Of these 38 the lesion in the liver was periportal 26 times; in 3 the lesion was intra-acinal, and in 9 the lesions were both periportal and intra-acinal. In the 7 cases showing no ulcers in the intestines there were periportal tubercles in 2, intra-acinal in 3, and both periportal and intra-acinal in 4 cases. It seems likely, from the findings in these cases, that the infection generally comes from the intestine via the portal vein, but in all probability it does come also from the general circulation by way of the hepatic artery. In 2 cases of acute miliary tuberculosis the tubercles were found in the portal spaces, and also scattered throughout the parenchyma, and it is probable, as asserted by Zehden, that the infection in acute tuberculosis comes by way of the hepatic artery.

Solitary Tubercles.—Under this heading we include all the large caseous masses occurring in the liver, whether single or multiple. This is a very constant finding in tuberculosis of birds, where it is the only organ attacked in 20 per cent. According to Hutchinson, tuberculosis of the liver was absent but twice in a series of 25 cases of avian tuberculosis. It occurs also very often in the livers of monkeys and cattle.

Under this heading we have two subdivisions: (1) Conglomerate tubercles. (2) Tuberculous cavities or bile-duct tubercles.

By conglomerate tubercles is meant the collection of large caseous masses which we sometimes find in the liver. It is simply a collection of solitary tubercles. Craven Moore reports a case of conglomerate tubercles in the liver of a case of cancer of the stomach, and thinks that the infection came in through the ulcerated surface in the stomach. Orth reported two cases, but it was before the discovery of the tubercle bacillus, and the diagnosis was disputed by Zehden and Simmonds, who think he had to deal with either a gumma or a cancer. Other cases are reported by Simmonds, Rolleston, MacKenzie, Anderson, Middleton, and Clement. In most of these cases the initial tuberculosis was in the bones, and in the case reported by Middleton there were solitary tubercles in the brain of the patient, who was a child of three. This variety of tuberculosis seems more apt to occur in children than in adults. The centers of the nodules may undergo softening, in which event we have the appearance of a cavity with caseating walls.

The bile-duct tubercles are so called because of their association with the bile-ducts, and it was claimed by Virchow that the bile-ducts are occluded by tubercles and cysts formed. It has also been thought that the infection comes from the intestines by way of the bile-ducts. Both these theories seem to be in error. Instead of the bile-ducts being occluded, it is likely that the center of a tubercle caseates and breaks into a bile-duct, and the cavity thus formed becomes stained with bile.

Simmonds thinks that the infection travels up the bile-duct, but Sergent, Kotlar, and Sabourin think that it reaches the liver by the portal vein and then involves the duct by extension, breaks into it, and may infect the duct and travel along it. Cases of bile-duct tubercle are reported by Simmonds, Hare, Wethered, and MacKenzie. In this series we have but one case showing solitary tubercles. The lesions were multiple, and averaged about 1½ cm. in diameter, did not exhibit any tendency to cavity formation, and were associated with miliary tubercles.

Tuberculous Cirrhosis.—Cirrhosis of the liver may accompany tuberculosis and be due to an entirely independent cause. For instance, we may have an alcoholic cirrhosis, superimposed upon a tuberculous infection, or cirrhosis of the liver with tuberculosis elsewhere in the body, but it has long been felt that there was a fibrous hepatitis due to the tubercle bacillus. Briege, in 1879, described a fibrous hepatitis occurring in tuberculous patients, with the formation of fibrous tissue which inclosed the lobules, together with newly formed bile-ducts. Arnold also speaks of newly formed bile-ducts.

Rolleston quotes Hanot and Gilbert, who describe a large fatty liver with a small-cell infiltration and fibrous hyperplasia of the portal spaces, together with miliary tubercles. This they call "hypertrophic fatty tuberculous hepatitis." The same authors describe two other forms: (*a*) Cirrhosis without any enlargement of the liver. (*b*) Cirrhosis with more fibrous tissue than the variety just mentioned, but with similar fatty change and tuberculous infiltration. The two latter forms differ only in the fact that one shows nodules, like those seen in cirrhosis with adenomata. Rolleston thinks that these forms occur, but he does not think them tuberculous. He thinks it reasonable to suppose the tubercle bacillus capable of a sclerogenic effect in the liver.

In animals, as in guinea-pigs, Hanot and Gilbert were able to produce a cirrhosis of the liver by the infection of avian tubercle bacilli, while human bacilli produced fatty change or coagulation necrosis. Hanot found a deeply scarred liver, like that of acquired syphilis, associated with miliary tubercles. Collet and Gallivardin report a case of tuberculosis of the portal spaces with a delicate fibrosis accompanying. Craven Moore reports finding a typical hob-nailed liver in a rabbit injected with tubercle bacilli. The rabbit

lived for a year after the injection and improved, and at the autopsy showed nodules in the lung, and the condition of hepatic cirrhosis. Mixed infection, according to Rolleston, may set up a gastritis and a consequent dyspeptic type of cirrhosis. A marked grade of passive congestion may set up a cirrhosis—so-called cardiac cirrhosis. In our series there was a slight increase of fibrous tissue in 7 cases, and there was 1 well-marked case of atrophic cirrhosis. How much influence the tuberculous infection has on the production of fibrous tissue we are not prepared to say.

Coincident Pathological Processes.—1. *Amyloid Degeneration.*—This is a more or less frequent occurrence in chronic tuberculosis, not only of the lungs, but also of the bones. In this series it was found ten times, or 10 per cent.

2. *Fatty Change.*—This condition has been the subject of much discussion. Langerhans thinks that it is due to a paralysis of the hepatic cells, and that the fat which is physiologically stored there is not given up. Klebs thinks it is the direct result of the tuberculous process on the lymphatic apparatus of the liver, the lymph outflow being hindered and the fat retained. In our series it was present in 35 cases, or in 35 per cent.

3. *Congestion.*—The occurrence of congestion is an almost constant finding. In chronic lung disease the embarrassed respiratory apparatus, with its effect upon the right heart, sooner or later gives rise to passive congestion. The liver is one of the first organs to show this change. In our cases there were 25 cases of slight congestion, 47 of moderate, and only 22 of severe. In 6 cases congestion was not present.

Conclusions.—1. Miliary tubercles are found in the great majority of the livers of the cases of chronic phthisis coming to autopsy.

2. Solitary tubercle of the liver is a very rare manifestation.

3. The infection probably is hematogenous, the bacilli being carried to the liver by the portal vein and the hepatic artery.

4. Passive congestion of the liver is found in nearly every case of pulmonary tuberculosis, while amyloid and fatty change are found in a relatively small number of cases.

5. From our cases we are not convinced that a fibrosis or cirrhosis of the liver due to the tubercle bacillus does occur, and are more inclined to believe that the fibroses found are due to other etiological factors.

REFERENCES.

Anderson: The Australian Medical Gazette, March 20, 1899.
Arnold: Virchow's Archiv, Bd. lxxxii, 1880.
Bar and Renom: Soc. de Biologie, June 29, 1895.
Baumgarten: Zeitschrift für klin. Med., Bd. ix and x.
Briege: Virchow's Archiv, Bd. lxxv, 1879.
Brissard and Loupet: Études exp. sous la direct du Prof. Verneuil, i, Paris, 1887.

Bristowe: Trans. British Path. Soc., vol. ix, 1858, p. 241.
Clement: Virchow's Archiv. Bd. cxxxix, S. 35.
Collet and Gallivardin: Archiv. de med. exp. et de Anat. path., March, 1901.
D'Arrigo: Centralblatt für Bakt., 1900.
Forster: "Handbuch der spec. pathologische Anatomie," 1854.
Fraenkel: Zeitschrift für klin. Med., 1892.
Gibbert and Lion: Soc. de Biologie, 1888.
Hanot and Gilbert: La Semaine Med., 1892.
Hanot and Lauth: Études exp. sous la direct du Prof. Verneuil, ii, Paris, 1888.
Hare: Trans. British Path. Soc., 1858.
Holmes: Boston Med. and Surg. Journal, 1841.
Hutchinson: "Studies in Human and Comparative Pathology," p. 304.
Klebs: Allg. Path., 1869.
Koeckel: Virchow's Archiv, Bd. cxliii, 1896.
Koester: Centralblatt für innere Med., 1896.
Kotlar: Zeitschrift für Heilkunde, Bd. iv, 1894.
Lancereaux: Traite des Maladies des Foie et du Pancreas, p. 662, 1899.
Louis: "Recherches sur la phthisie," Paris, 1843.
Mackenzie: Trans. British Path. Soc., vol. xli, p. 156.
Middleton: Glasgow Med. Journal, February, 1893.
Moore: Medical Chronicle, October, 1899.
Nocard: Revue de la Tuberculose, 1895.
Orth: Virchow's Archiv, Bd. lxvi, 1871.
Rolleston: "Diseases of the Liver."
Rosenberger: Trans. Phila. Path. Soc., vol. ix, 1906.
Sabourin: La Semaine Med., No. 85, 1891.
Sergent: Thèse Paris, 1895.
Simmonds: Centralblatt für allg. Path., November, 1898.
Simmonds: Deutsches Archiv für klin. Med., 1888.
Von Honl: "Acad. des Sciences de l'empereur Franz Joseph I," Bulletin International, Prague, 1895.
Wagner: Deutsches Archiv für klin. Med., Bd. xxxiv, 1884.
Waldenberg: "Die Tuberculose," Berlin, 1869.
Waring: "Diseases of the Liver."
Wethered: Trans. British Path. Soc., 1889.
White: Third Annual Report, Henry Phipps Institute, 1907.
Zehden: Centralblatt für path. Anat., vol. viii, 1897.

Le foie dans la tuberculose.—(Ullom.)

La tuberculose du foie se manifeste comme: 1. Tubercules miliaires. 2. Tubercules solitaires. 3. Cirrhose tuberculeuse.

1. Les tubercules miliaires du foie forment quelquefois la seule manifestation de la tuberculose congénitale, l'infection allant de la mère à l'enfant par la voie ombilicale. Chez l'adulte, l'infection peut venir jusqu'au foie par la veine porte, provenant d'un ulcère intestinal, ou de la circulation générale, par l'artère hépatique. Il paraît que dans la tuberculose chronique, l'infection vient par la veine porte et qu'elle passe par l'artère hépatique dans la tuberculose aiguë. On trouve des tubercules miliaires dans les foies de malades phthisiques qu'on a l'occasion de voir à l'autopsie, dans 50 à 80 % des cas. Dans la présente investigation ils furent trouvés dans 79 sur 100 cas. Le tubercules sont situés d'habitude autour des ramifications de la veine porte, quoique des fois on les trouve à l'intérieur du lobule. Dans notre série, ils étaient périportaux dans 50.6% intra-acineux dans

21.5% et périportaux et intra acineux en même temps dans 27.8%. Dans une série de 45 cas ayant des tubercules et qui furent examinés spécialement pour étudier la relation entre les tubercules et l'ulcération intestinale, les ulcères furent trouvés dans 38 cas et, parmi ceux-ci, la lésion était 26 fois périportale, 3 fois intraacineuse et en même temps périportale et intra-acineuse dans 9 cas. On peut conclure que l'infection d'au moins la majorité des cas vient de l'intestin par la veine porte.

2. Les tubercules solitaires sont une manifestation rare chez l'homme, mais très commune chez les oiseaux, les singes et les autres animaux inférieurs. On les trouve sous forme de grandes masses caséeuses et ils peuvent être seuls ou multiples. On n'en trouve qu'une fois dans cette série.

3. Cirrhose tuberculeuse: Plusieurs observateurs ont soutenu qu'il y avait une cirrhose du foie dûe au bacille de la tuberculose. Une cirrhose expérimentale a été produite par l'injection de bacilles et on trouve par hasard des cirrhoses chez des malades morts par la tuberculose; malgré cela, il paraît que l'existence d'une cirrhose tuberculeuse n'est pas prouvée.

Il y a trois procès pathologiques coïncidents trouvés dans le foie, dans les cas de tuberculose: dégénérescence, amyloïde, dégénérescence graisseuse et congestion passive. L'amyloïde fut trouvé dans 10% de nos cas, la dégénérescence graisseuse, dans ses différents degrés, dans 35% et la congestion passive, dans différents degrés, dans 94%.

Conclusions.—1. Les tubercules miliaires se trouvent dans le foie de la majorité des cas de phthisie chronique qui viennent à l'autopsie. 2. L'infection est probablement hématogène, les bacilles arrivant au foie par la veine porte et par l'artère hépatique. 3. Les tubercules solitaires du foie sont très rares chez l'homme. 4. La congestion passive du foie se trouve dans presque tous les cas de tuberculose pulmonaire, tandis que les dégénérescences amyloïde et graisseuse ne se trouvent que dans un nombre relativement petit des cas. 5. De nos cas, nous n'avons pas pu nous convaincre qu'il existe une fibrose ou une cirrhose du foie dües au bacille de la tuberculose et nous pensons plutôt que les fibroses qui ont été trouvées, sont dûes à d'autres causes.

Die Lebertuberkulose.—(Ullom.)

Die Tuberkulose zeigt sich in der Leber als: 1. Miliartuberkel. 2. Einzel-Tuberkel. 3. Tuberkulöse Lebercirrhose.

1. Miliartuberkel in der Leber sind manchmal das einzige Zeichen einer angeborenen Tuberkulose, da die Infektion von der Mutter zum Kinde durch die Nabelvene reist. Im Erwachsenen kommt die Infektion entweder von einem Darmgeschwür vie der Pfortader, oder durch die Leberarterie von der allgemeinen Circulation. In der scharfen Tuberkulose

kommt die Infektion wahrscheinlich durch die Leberarterie, und in der chronischen durch die Pfortader. Miliartuberkel werden in den Lebern der zu Sektion kommenden Tuberkulösen in von 50 bis 80% nach verschiedenen Beobachten sich verändernden Fällen. In dieser Untersuchung wurden sie neunundsiebzigmal in einhundert Fällen gefunden. Sie befinden sich gewöhnlich um der Pfortader herum, obwohl manchmal auch im Läppchen. In unserer Serie waren sie periportal in 50.6%, intra-acinös in 21.5%, und periportal und intra-acinös in 27.8%. In einer Serie von 45 Tuberkel zeigenden Fällen, die mit besonderer Hinsicht auf Darmgeschwüre untersucht wurden, fand man Geschwüre in 38, und von diesen 38 Fällen war die Läsion 26 mal periportal, 3 mal intra-acinös, und 9 mal periportal und intra-acinös. Von diesen Bemerkungen halte ich es für billig, zu beschliessen, dass die Infektion, wenigstens in den meisten Fällen, vom Darm via der Pfortader kommt.

2. Einzel-Tuberkel: Dieses ist eine seltene Erscheinung beim Menschen, kommt aber häufig in Vögeln, Affen, und anderen Tieren vor. Sie werden als grosse, käsige Konglomerate entweder einfach oder mehrfach gefunden. Sie wurde nur einmal in dieser Serie beobachtet.

3. Tuberkelcirrhose: Eine Anzahl Beobachter haben behauptet, es gäbe eine vom Tuberkelbazillus stammende Lebercirrhose. Eine Cirrhose ist experimental durch die Einspritzung von Tuberkelbazillen verursacht worden, und Cirrhosenfälle hat man manchmal in ander Tuberkulose sterbenden Kranken gefunden, aber es ist nicht bewiesen worden, dass es eine tuberkulose Lebercirrhose giebt.

In der Lebertuberkulose sind drei zusammentreffende Krankheitsprozesse vorhanden, namentlich: Amyloidleber, Fettleber, und Stauungsleber. Amyloidleber wurde in unserer Serie in 10% der Fälle, Fettleber in verschiedenem Grade in 35%, und Stauungsleber in verschiedenem Grade in 94%; nur sechs Fälle zeigten keine Stauung.

Schluss.—1. Miliartuberkel werden in den Lebern der meisten chronischen Tuberkulösen, die zum Sektionstisch kommen, gefunden.

2. Die Infektion ist wahrscheinlich hämatogen, indem die Bazillen durch die Pfortader und die Leberarterie in die Leber getragen werden.

3. Einzellebertuberkel kommt bei Menschen sehr selten vor.

4. Die Stauungsleber befindet sich in fast jedem Lungentuberkulösen, aber Amyloidleber und Fettleber findet man verhältnissmässig selten.

5. Durch unsere eigene Erfahrung sind wir nicht überzeugt, dass eine vom Tuberkelbazillus verursachte Leber-Sklerose oder Cirrhose vorhanden ist, und sind mehr geneigt zu glauben, dass die fibrösen Veränderungen, die man zuweilen beobachtet, auf andere als ätiologische Momente zu beziehen sind.

TUBERCULOSE ET CAPSULES SURRÉNALES.

Par Prof. E. Boinet,
Marseille.

La tuberculose atteint assez fréquemment les capsules surrénales. L'altération la plus importante est la tuberculose chronique surrénale, à forme casséeuse massive, qui se traduit cliniquement par la Maladie d'Addison classique. Il existe encore des lésions surrénales attenuées (tubercules, foyers casséeux isolés, scléro-tuberculose, cirrhose capsulaire) qui correspondent à des modalités cliniques peu accentuées du syndrome addisonnien. C'est à ces faits que nous avons donné par abréviation le nom d'Addisonisme, établissant ainsi une analogie comparable à celle qui existe entre le mal de Bright et le Brightisme. Tandis que dans la maladie d'Addison, la tuberculose capsulaire chronique est le plus souvent primitive et la tuberculose pulmonaire exceptionnelle, dans l'Addisonisme, au contraire, la phtisie avancée est la règle et les lésions surrénales ne sont que secondaires et tardives.

I. Maladie d'Addison. Aux observations que nous avons déjà publiés* nous ajouterons les faits suivants:

Madame X, agée de 29 ans, sans traces de lésions pulmonaires, entre dans notre service de clinique médicale de l'Hôtel-Dieu pour une maladie bronzée d'Addison dont le début remontre à neuf mois. La mélanodermie, la pigmentation des muqueuses sont considérables et l'asthénie est très accusée. En raison des accidents mortels† que nous avons observés à la suite d'injections sous-cutanées d'adrénaline chez des Addisonniens, nous n'administrons quotidiennement à cette malade par la voie stomacale que dix gouttes d'une solution d'Adrénaline normale. Le troisième jour, elle est prise de douleurs abdominales, de vomissements, de diarrhée abondante; puis ces phénomènes d'insuffisance capsulaire aiguë augmentent promptement d'intensité, l'état général s'aggrave; le lendemain, la torpeur s'accentue, la malade tombe dans le coma et elle succombe, le surlendemain, avec tout le syndrome de l'insuffisance surrénale et tous les signes d'une auto-intoxication rapide.

Autopsie. On voit une congestion très intense, extraordinaire de tous les organes. Les poumons ont une coloration rouge brun, et sont extrém-

* Archives générales de Médecine, 1903, 1904; dans les Congrès de Médecine interne Lyon 1894, Bordeaux 1895, Montpellier 1898, dans le Congrès des Sociétés savantes, 162, 498, 646; 1896, p. 364; 1897, p. 466; 1899, pp. 671, 673. Congrès de Médecin tenu à la Sorbonne 1897; les Bulletins de la Société de Biologie 1895, 1896, 1897, 1899, et de l'Académie de Médecine de Paris 1907.

† La mort dans la Maladie d'Addison (Archives Générales de Médecine Paris, 1903, pp. 321–345. Du Tremblement provoqué ou exagéré par l'opothérapie surrénale (do. 1903, pp. 982–990). L'Addisonisme (do. 1904, No. 37 et 40).

ment hyperhémiés; ils ne présentent aucun tubercule. Le coeur est mou, sans lésions valvulaires; il existe d'abondants caillots dans les cavités droites. La face interne de l'aorte est couverte de suggillations rouge vif dues à une imbibition sanguine. La rate est volumineuse, rouge brun, diffluente; le foie est augmenté de volume, a une coloration chamois; ses coupes offrent une teinte rose de dégénérescence. La bile est peu abondante, épaisse, olivâtre. Toute la masse gastro-intestinale est le siège d'une forte congestion avec de nombreuses suggillations. Le pancréas est rouge, congestionné. Les reins présente une congestion considérable, en masse. Cette énorme hyperémie d'origine toxique existe au niveau des centres nerveux et en particulier sur le bulbe, les plexus, les ventricules, les corps opto-striés et le cervelet. Le corps pituitaire, le corps thyroïde sont normaux. Seules les capsules surrénales présentent des lésions tuberculeuses. Dans la capsule surrénale droite, on trouve un gros foyer casséeux, du volume d'une noisette, au niveau de son extrémité interne et un autre noyau casséeux, ayant les dimensions d'un pois et entouré d'une substance rouge brun, congestionnée. La capsule surrénale gauche a un tiers de plus que son volume normal; elle est infiltrée dans toute son épaisseur de gros noyaux casséeux.

Cette transformation caséo-tuberculeuse massive primitive des deux capsules surrénales existait encore dans une série d'observations dont on trouvera la relation dans notre mémoire sur la mort dans la maladie bronzée d'Addison.

Dangers des injections d'Adrénaline, utilisé de l'extrait surrénal glycériné. Les Addisonniens, qui font l'objet des observations V et VI, succombèrent deux jours après une injection sous-cutanée d'un tiers de milligramme d'adrénaline faite le lendemain d'une trop longue marche. La médication par l'extrait glycériné de capsules surrénales de veau est préférable comme le prouve le cas suivant: Lag. présentait, il y a dix ans, tous les signes classiques de la maladie bronzée d'Addison. Il fut soumis a un traitement intensif. L'abus des injections sous-cutanées d'extrait glycériné surrénal fut suivi de tremblement.* Depuis cette époque, il a continué son traitement. Actuellement, la pigmentation cutanée et muqueuse a fortement diminué, l'asthénie a presque disparu, il peut faire de longues marches, il a engraissé d'une vingtaine de Kilogs. Cette amélioration extraordinaire, qui se maintient depuis dix ans, équivant presque à une guérison et à ce point de vue, ce cas est bien plus probant que celui de Béclère qui n'a suivi son malade que pendant trois ans et surtout que ceux de Schilling, Anderodias, Hirtz dans lesquels la guérison est bien douteuse.

Une amélioration très marquée à été encore obtenue par l'ingestion stomacale d'Elixir de capsules surrénales de veau chez une femme agée de

* Boinet: Troubles nerveux et Tremblement observés chez un addisonnien à la suite de trop fréquentes injections d'extrait de capsules surrénales (Société de Biologie 11 Novembre, 1899, p. 891); Du Tremblement provoqué ou exagéré par l'opothérapie surrénale (Archives générales de Médecine Paris, 1903, pp. 982–990). Réunion Biologique de Marseille, Société de Biologie et Academie de Médecine, Paris, 1903.

60 ans atteinte de maladie d'Addison. Ces bons résultats se maintiennent depuis six ans.

Tremblement opothérapiqué surrenal.—Le tremblement déterminé par la médication surrénale appliquée à doses exagérées aux Addisonniens, présente un intérêt pratique, car il indique que la dose médicamenteuse d'extrait surrénal ou d'adrénaline est dépassée; il fournit, en outre, notions utiles au diagnostic, au pronostic et au traitement.

C'est ainsi que l'apparition d'un tremblement consécutif à l'opothérapie surrénale peut servir d'élément de diagnostic dans les cas douteux, dans les formes frustes de maladie d'Addison, dans certaines variétés de mélanodermie. Ce tremblement est surtout accentué dans la maladie d'Addison avec lésions caséo-tuberculeuses étendues des deux capsules surrénales comme dans le cas de tuberculosis, ajusteur mécanicien qui fait l'objet de l'observation II de notre mémoire sur le tremblement surrénal et dans l'observation V de notre travail sur la Mort dans la Maladie d'Addison publié en 1903, dans les Archives générales de Médecine de Paris. Nous y faisions remarquer que ce tremblement opothérapique s'était produit rapidement et avait été surtout prononcé, dès les premiers injections de produits surrénaux chez les Addisonniens qui avaient été ensuite notablement améliorés par ce traitement. Nous insistions encore sur les modifications circulatoires et thermiques observées, en pareil cas. Ces injections sous-cutanées d'extrait glycériné surrénal ou d'adrénaline diminuaient le nombre des pulsations radiales et augmentaient la pression artérielle d'une quantité équivalente à une division du sphygmomanomètre Verdin (14 au lieu de 13). Nous proposions, à cette époque, d'utiliser ces dernières données pour le diagnostic de la maladie d'Addison. Quatre ans plus tard, dans une communication faite le 23 Avril 1907 à la Société Médicale et Chirurgicale de Londres, Grunbaum disait qu'en faisant ingérer 3 fois par jour, pendant 3 jours, 18 centimètres d'extrait surrénal, on observe une élévation marquée de la pression sanguine, s'il existe une maladie d'Addison, à condition toutefois que le sujet soit indemne de toute lésion valvulaire.

Enfin l'hyperthermie consecutive aux injections sous-cutanées de produits surrénaux qui, dans un de nos cas, atteignait deux degrés au bout d'une demi-heure pour retomber à la normale, mais qui ne s'élevait plus que d'un degré dans la suite, peut constituer un signe de diagnostic en faveur de la maladie d'Addison. Cette élevation momentanée de température était en rapport avec l'intensité du tremblement de provenance opothérapique; elle est comparable à l'hyperthermie que provoque l'injection de tuberculine chez les tuberculeux. Il serait intéressant de faire des recherches dans ce sens d'autant plus que l'autopsie d'un de ces Addisonniens tuberculose révéla en même temps que des altérations fibro-caséeuses étendues des deux capsules surrénales l'existence, au sommet du poumon droit, d'un noyau fibreux, crétacé et caséeux, gros comme un abricot, vestige d'une tuberculose cicatrisée.

Etiologie. Age. À propos de l'étiologie de la maladie d'Addison qui se developpe presque toujours avant la quarantine, nous relevons que 4 de nos malades avaient 42, 44, 55 et 60 ans.

Sexe. Les statistiques les plus récentes accusent la proportion de huit hommes pour une femme (Martineau, Chatalain, Chesneau) nous relevons dans nos observations de maladie d'Addison le chiffre d'un tiers de femmes.

Pathogénie. Au point de vue de la pathogénie, nous restons partisans de la théorie mixte que nous avons développée dans la Revue de Médecine (Paris, 1897, p. 136). Il est probable que la section surrénale agit sur le système nerveux pour régulariser la fonction pigmentaire. La clinique, l'anatomie pathologique et l'expérimentation sont favorables à cette théorie que confirment encore les cas de maladie d'Addison expérimentale, de maladie pigmentaire, que nous avons déterminée chez les rats d'Egout en cautérisant leurs capsules surrénales superficiellement et profondément avec diverses substances caustiques et en injectant dans leur épaisseur des cultures attenuées de tuberculose humaine.*

Ces faits expérimentaux servent de transition naturelle entre la maladie d'Addison et les pigmentations de la peau et de la muqueuse buccale que l'on observe chez les tuberculeux cachectiques et dans un certain nombre de cas de la maladie des vagabonds.

II. Mélanodermie Avec Taches Pigmentées de la Muqueuse Buccale chez les Tuberculeux Cachectiques.

1. Cette pigmentation anormale de la peau et des muqueuses chez les tuberculeux avancés est bien connue au point de vue clinique, et s'accompagne habituellement d'asthénie, de douleurs dorso-lombaires, en un mot, des signes d'une petite insuffisance surrénale. Les taches brunes de la muqueuse buccale sont pour ainsi dire la signature des lésions du plexus solaire, des splanchniques (Laiguel-Lavastine†) et des capsules surrénales (Boinet‡). Au point de vue pratique, la présence de plaques brunes de la muqueuse buccale comporte un pronostic assez fâcheux et indique une infériorité de résistance qui ne se vérifie que trop souvent, quand ces tuberculeux sont atteints de complications, de grippe, de pneumonie en particulier.

2. En dépouillant le protocole des autopsies de 267 tuberculeux adultes décédés dans notre service et ayant présenté 37 fois le syndrome addisonnien atténué précédemment indiqué, nous relevons douze fois des lésions tuberculeuses macroscopiques des capsules surrénales: petits noyaux caséeux (4 cas); foyers caséo-fibreux indurées (2 cas); tubercules isolés (5 cas);

* Boinet: Maladie d'Addison expérimentale chez le rat de Egout (Bulletin de la Société de Biologie, Paris, 1896, p. 164; 1897, pp. 439, 473) et Recherches expérimentales sur l'ablation des capsules surrénales (Société de Biologie, Paris, 1895, pp. 162, 498, 646; 1896, p. 364; 1897, p. 466; 1899, pp. 671, 673. Congrès de Médecine interne Lyon 1894, Bordeaux 1895, Montpellier 1898. Congrès des Sociétés savantes, Paris 1897, p. 260.

† Laiguel-Lavastine: Archives générales de Médecine, 1904, No. 40, p. 2497.

‡ Boinet: L'Addisonisme. Archives générales de Médecine, 1904, Nos. 37 et 40.

abcès caséeux (1 cas). Dans les autres observations, il existait presque toujours des altérations macroscopiques de surrenalite chronique et de sclérose de la couche corticale des capsules surrénales, c'est à dire de la zône capsulaire présidant à la fonction pigmentaire et riche en ganglions et fibres du grand sympathique. Les adhérences péri-capsulaires, fréquentes en pareil cas, expliquant les altérations concomitantes du plexus solaire. Dans un cas, la capsule surrénale droite était fibro-caséeuse et mesurait 9 centimètres de longeur sur 4 de largeur. Chez un tuberculeux cavitaire agé de 51 ans atteint de mélanodermie avec taches brunes de la muqueuse buccale, les capsules surrénales volumineuses mesurant 6 centimètres sur 3, sclérosées, parcourues par des sillons et des tractus longitudinaux, présentaient à la surface une série de petits tubercules. Dans un troisième cas, les capsules surrénales dures, scléreuses, cirrhotîques offraient quelques granulations miliaires superficielles; et mesuraient l'une 6 centimètres sur 2, l'autre 7 sur 4. Ces surrénalites chroniques scléreuses présentaient aussi des petites granulations, jaunâtres, parfois adénomatentes, donnant à la surface un aspect grenu et irrégulier. Nous citons à titre d'exception le cas d'une femme de 72 ans, atteinte de mélanodermie marquée avec taches noirâtres sur le visage et le dos des mains et offrant des plaques brunes sur la muqueuse buccale, à l'autopsie de la quelle nous notons l'absence de tuberculeuse pulmonaire, la présence d'un semis de tubercules jeunes sur la rate, l'existence d'une surrénalite chronique avec tubercules centreux dans la capsule surrénale gauche. Chex un homme 33 ans et chez une femme agée de 35 ans, ayant succombé à une poussée de granulie dans les principaux organes et à une meningite tuberculeuse, la présence de tubercules miliaires à la surface des capsules surrénales ne s'accompagnait pas de mélanodermie, en raison de la rapidité de l'évolution de la maladie.

3. Les lésions Histologiques que nous avons indiquées dans les mémoires précédemment cités et que nous avons constatées plus récemment sont conformes aux conclusions de Bernard et Bigard, de Parisot et Lucien* de Babès.†

Nos recherches anatomo-pathologiques et cliniques premettent donc d'établir une relation étiologique et pathogénique entre les altérations scléreuses et tuberculeuses attenuées des capsules surrénales et la mélanodermie avec taches brunâtres de la muqueuse buccale des tuberculeux cachectiques et de l'addisonisme, en général.

4. La pigmentation anormale de la peau de la muqueuse buccale avec petite insuffisance surrénale existait 20 fois sur 125 cas de tuberculose sénile, de tuberculeuse fibreuse, de tuberculose coexistant avec un état

* Parisot et Lucien: Étude physiologique et anatomique des capsules surrénales chez les tuberculeux. Réunion Biologique de Nancy (11 Novembre 1907).

† Babès: Lésions des capsules surrénales dans la tuberculose (Réunion Biologique de Bucarest) (23 Janvier 1908).

athéromateux prononcé de l'aorte*; elle correspondait anatomiquement à des lésions scléreuses ou tuberculeuses des capsules surrénales. Dans 6 faits, l'autopsie montra des petits tubercules à la surface des capsules et des foyers caséeux dans leur profondeur. La sclérose marquée des capsules surrénales est la lésion la plus fréquente. Enfin, dans les cas où l'athérome était notable, on constatait, en outre, une surrénalite chronique avec hypertrophie, hyperplésie, sclérose, cirrhose avec tractus fibreux limitant des petites granulations superficielles.

III. Maladie des Vagabonds.—Quand la mélanodermie phtiriasique s'accompagne de taches pigmentées sur la muqueuse buccale comme dans les cas publiés par Thibierge, Besnier, Chaffuard, etc., et dans nos observations personnelles, on ne peut guère invoquer logiquement l'action exclusive de l'irritation cutanée par les parasites et le grattage. Ces miséreux que la proximité du Chauffoir Municipal fait affluer dans notre service de l'Hôtel-Dieu sont en outre, souvent atteints de tuberculose fibreuse sénile, torpide, latente, parfois difficile à dépister, d'une asthénie considérable, d'une diarrhée profuse et rebelle. Habituellement l'autopsie permet de constater des lésions fibro-caséeuses avec ou sans cavernes de date ancienne, des ulcérations intestinales surtout localisées dans le caecum et le gros intestin et des altérations scléreuses quelquefois avec tubercules des capsules surrénales. Il est possible que cette sclérose capsulaire cette surrénalite chronique soit provoquée, en partie, comme certaines cirrhoses tuberculeuses du foie, par l'action de la toxine tuberculeuse. Il s'agit vraisemblablement, dans certains de ces cas particuliers, d'une sorte de tuberculose inflammatoire atteignant les capsules surrénales et comparable, à certains points de vue, à la forme décrite par Poncet. Du reste, ces scléroses surrénales se retrouvent surtout dans les cas où l'autopsie de ces miséreux montre une périviscérité fibreuse (avec adhérences séreuses et prolongements, à l'intérieur, des tractus superficiels) de la plupart des organes thoraciques et abdominaux. Quoiqu'il en soit, la fréquence relative des altérations scléreuses surrénales (qui existaient 65 fois sur 125 cas de tuberculose pulmonaire coexistant avec l'athérome aortique) porte à rattacher à une origine surrénale ces taches brunes addisonniennes de la muqueuse buccale et l'asthénie dans laquelle succombent ces miséreux. On le voit, suivant l'étendue, la profondeur, la variété anatomique des lésions surrénales, la tuberculose détermine soit la maladie d'Addison et le syndrome surrénal complet soit des formes plus légères dans lesquelles la mélanodermie, la pigmentation de la muqueuse buccale, l'asthénie, et les altérations capsulaires sont attenuées au point de légitimer le terme abréviatif d'addisonisme.

* Boinet: Tuberculose pulmonaire et athérome aortique (Académie de Médecine Paris, 1907). Fréquence et Danger de la Tuberculose sénile (Marseille Médical no. 16, Août 1905). Maladies de l'arote (Traitè de Médecine de Brouardel et Gilbert. Fasciale 23. 2 Edition 1906, p. 416).

THE PRESENT STATE OF OUR KNOWLEDGE CONCERNING HEREDITY IN TUBERCULOSIS.

By Aldred Scott Warthin, Ph.D., M.D.,
Professor of Pathology and Director of Pathological Laboratory, University of Michigan, Ann Arbor.

The once dominating belief in the heredity of tuberculosis has, in the years following the discovery of the tubercle bacillus, almost ceased to play any important part in discussions concerning the etiology of the disease. As soon as Koch's bacillus became accepted as the causal agent, the idea of a true inheritance of tuberculosis was of necessity abandoned. To the few adherents of the doctrine of parental influence as an important etiological factor there remained, however, four theories by which the congenital occurrence of tuberculosis or a congenital predisposition to tuberculosis became possible: (1) the direct transmission of the tubercle bacillus through the sperm or ovum (germinative or conceptional infection); (2) the passage of the bacillus from the maternal blood through the placenta to the fetus (placental infection); (3) the transmission of toxins or abnormal products of metabolism from the maternal blood through the placenta to the fetus (acquired congenital predisposition); (4) the transmission through the germ-cell from one or both parents of an intrinsic susceptibility or predisposition to postnatal infection with the bacillus. Of these four possibilities of parental influence, the prenatal transmission of the bacillus or of the toxins is but a pseudo-inheritance and not a true heredity. Indeed, as Lubarsch has already described it, it is but a metastasis from one individual into another. On the other hand, the transmission of an intrinsic susceptibility is a true heredity. Therefore the old conception of the heredity of tuberculosis now appears clothed in the new garments of an inheritance of an intrinsic predisposition to the disease and not an inheritance of the disease itself.

To tuberculosis resulting from the parental transmission of the bacillus we must apply the term congenital and not inherited. Nevertheless in our journals and text-books of the present day these terms are interchangeably and synonymously used. This loose use of these words should be discouraged. Only that which develops from the determinants of the sexual nuclei can be regarded as inherited. To this criterion must we restrict our conceptions of heredity. The transmission of bacilli or toxins in the germ-cells or through the placenta gives rise to congenital tuberculosis, congenital predis-

position or congenital immunity, as the case may be. Having thus stated at the outset that there can be no heredity of tuberculosis itself, our conception of this phase of the tuberculosis problem becomes narrowed down to the inheritance of a predisposition to the disease.

In spite of the almost universal belief in postnatal opportunities for infection as constituting the etiological factor of chief moment, voices have been raised here and there asserting that inherited predisposition to tuberculosis is of equal or greater importance. Just at present it appears that the number of these voices is increasing, and it seems probable that the doctrine of intrinsic inherited predisposition to tuberculosis is destined to increasing prominence in the immediate future. It may, therefore, be worth while for us to consider here the grounds that exist in support of this view. Before doing this our knowledge concerning the different forms of congenital tuberculosis may be briefly outlined under the heads of "congenital tuberculosis" and "congenital predisposition to tuberculosis."

I. Congenital Tuberculosis.

(*a*) *Germinative or Conceptional Tuberculosis.*—Theoretically a germinative transmission of tubercle bacilli may occur on the part of either father or mother; but up to the present time no absolutely proved observation of this occurrence in man has been recorded. Nevertheless, much evidence has been already collected proving absolutely many of the conditions essential to such a transmission, so that theoretically we must accept it as a possibility and await its positive demonstration. For example, on the paternal side the presence of tubercle bacilli in the semen of men suffering with genital tuberculosis, as well as in that of men having pulmonary tuberculosis without local lesions of the genital tract, has been demonstrated by numerous observers (Spano, Dobroklowski, Jani, Aubeau, Jäckh, Nakarai, Simmonds, and others). According to Nakarai, virulent tubercle bacilli are found in small numbers in the semen of men dying of pulmonary tuberculosis but without lesions of the genital tract. Similar observations on animals have also been recorded (Gärtner, Maffuci, etc.). Further, Schuchardt and Schütt have demonstrated the occurrence of a tuberculous catarrh of the urethra, the bacilli being present in the secretions in large numbers. A number of clinical observations tend to prove that the genital tract of the female may be infected by tuberculous semen. While tubercle bacilli have not yet been observed in spermatozoa, the experimental work of Friedmann gives us good reason to believe that such an occurrence is possible. He proved that tubercle bacilli injected into the vagina of rabbits immediately after copulation could pass into the embryos; and further that tubercle bacilli could also be found in the embryos arising from male animals into whose seminal ducts,

testes, or blood-vessels tubercle bacilli had been injected a few weeks before copulation.

In so far as the positive demonstration of the occurrence of a germinative transmission from the mother is concerned, we are likewise without conclusive observations. The ovum may be infected in two ways, either while in the ovary or after leaving it. The intra-ovarian infection has been positively demonstrated. Tuberculosis of the ovary has been shown to be of much more frequent occurrence than was formerly supposed. Schöttlander and others have demonstrated the occurrence of tuberculosis of the follicles, and Sitzenfrey has observed tubercle bacilli in a human follicle and ovum. Friedmann's experiments have shown that an infected ovum may develop. Beyond these points our positive knowledge cannot take us at the present. Therefore, as far as man is concerned, an intra-ovarian infection of the ovum has been demonstrated; extra-ovarian infection has not been conclusively proved, but there are no observations that would make its occurrence seem improbable. Summing up the evidence for and against germinative conception in man, both paternal and maternal, complete proof of its occurrence is lacking, but what evidence bearing upon this point can be collected favors or, at least, does not tend to disprove the theory of such an occurrence.

(*b*) *Placental Transmission.*—Of this form of congenital tuberculosis we now possess a fairly full knowledge from the observations of Lehmann, Schmorl, Runge, Schmorl and Geipel, Warthin, Jung, Carl, Wollstein, Schrumpf, Sitzenfrey, etc. Over thirty cases of placental and decidual tuberculosis have now been observed and the passage of tubercle bacilli into the fetus conclusively demonstrated. These cases show that the condition cannot be so rare as it is commonly regarded, since the reported cases have been observed by a small group of investigators. Pregnancy in a tuberculous woman favors the entrance of tubercle bacilli into the blood-stream. Recent investigations would make us believe that in all cases of tuberculosis the bacilli gain entrance into the circulation. Chances would, therefore, favor their dropping out in the placental sinuses. As a result they may pass through the placenta into the fetus without causing local lesions in the former, or in case the bacilli lodge upon the endothelium of the decidual sinuses or upon the chorionic syncytium there results a local degeneration or necrosis followed by the formation of an agglutination-thrombus, which in turn may develop into a tubercle. From the placental lesions tubercle bacilli may pass into the fetus. In the fetal body they may excite the lesions of tuberculosis, or, as has been several times observed, the bacilli may be present in the fetal circulation in great numbers, without causing lesions. In the explanation of such a phenomenon we can but assume an immunity on the part of the fetus (aggressin immunity). The syncytium possesses no immunity to the tubercle bacillus, but on the contrary appears to be

easily damaged by the bacilli lodging upon it. Following the entrance of bacilli into the decidual sinuses five forms of placental tuberculosis may develop: (1) Decidual; (2) intervillous; (3) intravillous; (4) intravascular chorionic; (5) chorio-amniotic. From the chorionic lesions the decidual ones are distinguished by their failure to develop epithelioid and giant-cells.

Of the occurrence of this form of congenital tuberculosis and of the infection of the fetus through the placenta there exists abundant and detailed evidence, and of the pathology of placental tuberculosis we now possess satisfactory knowledge. The question of greatest importance concerning it yet to be settled is its frequency. At least, there can be no doubt that it occurs much more often than has been assumed, and the statements in our text-books concerning its negligible importance have been exaggerations in the wrong direction.

II. Congenital Predisposition to Tuberculosis.

The effects upon the fetus of the toxins and abnormal products of metabolism passed through the placenta of a tuberculous mother have been shown in animal experiments by a number of investigators. Carrière determined positively the injurious action of the toxins of the tubercle bacillus upon the embryo. The poison obtained by the result of extraction, and in still greater degree that contained in the residue of tubercle bacilli, have an injurious action upon the progeny when injected into the mother animal, and still greater when injected into both parents. The young obtained from such animals are fewer in number; many of them die *in utero* or shortly after birth or show signs of a constitutional weakness. Further, they show an increased susceptibility to inoculated tuberculosis, this susceptibility being also greater in those cases in which both parents had been inoculated with the toxins. Bandelaq de Pariente, Kobelin, Rivière, Bossi and others likewise assert the injurious effects of the toxins of tubercle bacilli upon the fetus. According to these writers, the fetus of a tuberculous mother may show signs of intoxication in various internal organs, the liver in particular. These changes are not of a specific character, but are common to many forms of intoxication, such as fatty degeneration, etc. As a result of these degenerations hemorrhages, rupture of blood-vessels, stasis, cirrhosis, etc., may occur. The source of the poisons may be sought not only in the toxins of the tubercle bacillus, but also in products arising from the cells of the maternal organism killed or damaged by the tuberculous process. The effect upon the fetus of the latter poisons may be a general cachexia or marasmus, leading to a general or partial hypoplasia. Such a condition of general or local weakness may predispose to tuberculous infection during the early months of life.

As to the specific character of such a predisposition, the majority of writers incline to the negative view. Nevertheless more recently the occur-

rence of a specific predisposition acquired during fetal life has been maintained by some writers. Although Cornet believed that bacterial proteins can pass through the placenta into the fetus and cause such injury that its death may result, he also held it to be possible that as the result of such a diffusion of bacterial toxins through the placenta into the fetal circulation an immunity against tuberculosis might be obtained in intrauterine life. Other writers hold a similar view. The aggressin theory has thrown new light upon this question. The principle as stated by von Herff, that all soluble substances, in the blood of either mother or fetus, that do not essentially damage the blood can pass from the maternal blood into the fetal, or the reverse, is probably to be accepted. The passage of the bacterial (tubercle) toxin can produce either a toxin immunity or can damage the fetal organism according to the amount of the toxin passed through into the latter. Should the tubercle aggressin alone pass the placenta, an aggressin immunity in the fetus against tuberculosis may be produced. In case both the toxin and the aggressin pass through, the results would vary with the amount; with small amounts of toxin and aggressin an immunity in the fetal organism would be produced; but in the case of large amounts the injurious action would be greater than in the case of the action of the toxin alone, since the formation of an antitoxin would be hindered by the aggressin. Still more dangerous to the fetus would be the entrance of tubercle bacilli into the fetal blood-stream with or shortly after the entrance of toxin and aggressin. In such cases a rapidly fatal tuberculosis of the fetus may occur, exactly comparable to the rapid death of guinea-pigs when injected with aggressin and tubercle bacilli simultaneously. The same thing could occur in the case of a new-born child of a tuberculous mother; the infantile organism containing tubercle aggressin received through the placenta in intrauterine life could develop a rapidly fatal tuberculosis in case tubercle bacilli entered its body soon after birth. On the other hand, the entrance of tubercle bacilli into the body of a fetus or new-born that had obtained an immunity against tuberculosis as the result of a diffusion of the aggressin into its blood would not result in the development of tuberculosis, or the latter would develop only after a long period of latency.

The aggressin theory, it will be seen, serves admirably to explain numerous observations that have been made relative to the effect of maternal tuberculosis upon the fetus. Negative and apparently contradictory findings can be harmonized by its application. Not only does it explain the occurrence of a specific congenital predisposition, but it throws an entirely different light upon the freedom from tuberculous infection or specific immunity observed in the new-born of some tuberculous mothers. The early development of tuberculosis in a certain proportion of such children is, therefore, to be expected when even the slightest opportunities for postnatal in-

fection are afforded by the conditions surrounding them. Further, a latency of a congenital infection becomes, according to this theory, an occurrence to be expected in certain cases. Baumgarten's view receives, through the application of this theory, a certain amount of support, in so far as his assumption of latency is concerned.

Summing up the exact and absolutely determined facts concerning congenital tuberculosis and acquired congenital predisposition, the placental transmission of the bacillus is the only form absolutely known to occur in the case of man. The germinative transmission and the intrauterine acquisition of a specific predisposition or immunity can with good reason be regarded as most probable events, although their complete demonstration is still lacking. To the researches of the near future must be left the filling-in of the present gaps in our knowledge concerning these extremely important problems. Nevertheless, a greater proportion of writers favor the theory of acquired congenital predisposition as an etiological factor of moment than those who uphold the importance of congenital infection. Baumgarten's view of the prime importance of congenital tuberculosis has certainly gained many facts tending to support it. We must all, however, concede that our knowledge of tuberculosis in general is opposed to any general acceptance of his view of the congenital transmission of the tubercle bacillus. For a certain proportion of cases such a transmission undoubtedly is true,—to what extent we do not now know, but I believe it is not a negligible proportion.

II. True Inherited Predisposition to Tuberculosis.

In entrance upon this part of the etiological problem we have to deal with assumptions and theories still more uncertain, and with no more substantial foundations than imperfect and meager statistics, or the individual opinions of certain clinicians or pathologists. There exist neither the results of animal experimentations nor clinical and pathological observations in man to give to such a theory a firm basis of support. Indeed, the great majority of clinicians follow Cornet in not recognizing inherited predisposition as an important factor, and in considering infection to be the essential if not the only element concerned in the etiology of tuberculosis. And, as I have already mentioned, the majority affirm this infection to be an extrauterine one, as opposed to Baumgarten's view.

There are not wanting, however, adherents to the theory of intrinsic predisposition, and Hüppe's dictum, that natural infection occurs only when the infecting organism enters the body of a susceptible individual of a susceptible race, has been gaining adherents, particularly with reference to tuberculous infection, as well as to certain other infectious diseases. It is a fact recognized by every one now that practically all adult bodies show at autopsy

evidences of healed tubercles. Into the bodies of us all, tubercle bacilli at times gain entrance. But not every individual, thus infected, develops the disease or, in case it does develop, dies from the infection. Otherwise tuberculosis would long ago have exterminated the human race. There can be no doubt also that tubercle bacilli enter the body-tissues in some individuals and remain there as potentially virulent and living organisms without exciting characteristic lesions of tuberculosis; indeed, in certain cases without producing any lesion that we can recognize as such. Between such infections with tubercle bacilli and the disease process, tuberculosis, it has in recent years been necessary to draw a definite line. Writers (Schlüter, etc.) have already begun to distinguish between the tubercle bacillus as an exciting agent, constituting only one etiological factor, and a general or individual tuberculosis anlage constituting the more important factor.

The existence of an individual predisposition, or weakened resistance to the tubercle bacillus, we cannot deny, and it is along the line of combating this susceptibility that our therapeutic and preventive attempts must be chiefly directed. In what this individual tuberculosis anlage lies we do not know at the present time, and we cannot even say positively how much of it is acquired and how much is really an inherited anlage, or whether it is a specific predisposition. Have we any data speaking in favor of the latter? Nothing positive. Animal experiments speak for the existence of a congenital specific predisposition, but experimental investigations have not yet been carried to the point where we can distinguish absolutely between the congenital predisposition that is inherited and that which is acquired in prenatal life. Statistics show the existence and importance of family predisposition, but even in those carefully analyzed groups of cases, in which paternal tuberculosis is made to appear of especial importance, we cannot now eliminate the factor of opportunity for infection. Failing to find any positive support in the results of animal experiments or in statistical studies, we may turn to pathological anatomy in search of positive evidence of intrinsic predisposition. And here we find certain observations adduced in favor of inherited predisposition. According to Bartel, general disturbances of development, associated with disturbances of development of the lymphatic system of the lungs in particular, form an anlage of predisposition to tuberculosis. Of such defective development of the lymphatic system, the status lymphaticus may be regarded as a manifestation. Other anomalies or disturbances of development, particularly hypoplasia of various organs or of the body as a whole, have also been regarded as constituting a tuberculosis anlage. Anatomical stigmata, such as hyperplasia of the mammary gland on the side primarily affected, have been regarded as evidences of congenital anlage. The same difficulty of proof attends all those theories, and we are unable to distinguish between intrinsic and acquired, cause and effect, etc.

Summing up the whole matter, we have no positive evidence of an intrinsic or inherited specific predisposition to tuberculosis. The reasons for the supporting of such a theory are to be sought in the minds of those who find no other possible explanation for the actual phenomena of the disease as seen clinically. The congenital transmission of the bacillus by the placental route is absolutely demonstrated, and we have excellent reasons for believing in congenital acquired predisposition, both general and specific. While we distinguish pathologically between this form of parental transmission and true heredity, we must not forget that many of the practical aspects of the question are identical in both cases. In our statements about the non-inheritance of tuberculosis we must include positive statements concerning congenital tuberculosis and a warning as to the dangers attending the progeny born of tuberculous mothers.

Proceedings of Joint Session of Sections I and II,

Opsonic Index. Conjunctival and Cutaneous Tuberculin Reactions. Serum Diagnosis.

JOINT SESSION OF SECTION I AND SECTION II.

Opsonic Index. Conjunctival and Cutaneous Tuberculin Reactions. Serum Diagnosis.

Tuesday Afternoon, September 29th, at half past two.

Sections I and II met in joint session in the large assembly hall of the New National Museum at half past two o'clock, on the afternoon of Tuesday, September 29th. The joint session was called to order by Dr. William H. Welch, President of Section I. Dr. Welch presided during the reading of the first five papers, with the discussion following, after which Dr. Vincent Y. Bowditch, President of Section II, took the Chair.

THE OPSONIC INDEX IN CERTAIN TUBERCULOUS INFECTIONS.

By Thomas Wood Hastings, M.D.,
New York.

In a study of the application of the opsonic index to clinical investigation and to therapy one should consider the four following factors:

1. The possibility of estimating an opsonic index.
2. The normal opsonic index and the variations found with normal serums. The variations found with serums from tuberculous individuals.
3. Variations found in the opsonic index in individuals not under tuberculin therapy.
4. Variations in the opsonic index in cases under tuberculin therapy.

The first and second may be dealt with briefly, since the factors referred to have been reported upon and established by several observers.

Since Wright's publication in the year 1903 it has been claimed by himself and his co-workers that one might obtain fairly constant results of clinical import by comparing the effect of normal and abnormal serums upon phago-

cytosis, with preparations carried out in vitro. Their claim has been that under the same conditions—that is, with the same bacterial suspension, exposed the same length of time and at the same temperature of the same serum—there is little variation in the number of bacteria taken up from the suspension by the phagocytic cells; that with different serums, provided the serums be obtained from healthy individuals, the phagocytic action is influenced in such a manner by these various "normal serums" that one obtains approximately the same degree of phagocytosis, estimated by counting the number of bacteria taken up from the suspension by phagocytes in vitro. A few observers—North and Park and Biggs in America, Reyn and Kjer-Petersen in Sweden—have maintained that constant results which would enable one to establish any normal standard are not to be obtained. The weight of evidence, judging from the amount of work done by a large number of observers, maintains Wright's contention, and recent articles in the Practitioner* confirm all the accuracy that Wright has claimed for his method. To one who has worked for a few years with Wright's methods and obtained results, not regardless of well-marked variations, it seems possible to estimate degrees of change in the power of serums which may be used for comparative purposes. Reyn and Kjer-Petersen, whose work was done with extreme care, obtained results which seemed either too high or too low, which could not be readily accounted for unless due to technic or to a real variation, and their "mean" error for an estimation with normal blood was 0.19. With cases of lupus the mean error was 0.25, a variation so little different from the normal that they could not accept it as pathological when comparisons were worked out on a mathematical basis. Their estimations were made daily or every second or third day over a period of six months, and their investigations led to no practical results.

We hesitate to accept their discouraging report on the use of tuberculin, for they did not give inoculations after the method found most useful, over long periods of time, by several careful observers. Any one who has worked with Wright's methods understands that occasionally preparations give unsatisfactory results, the main reasons being (*a*) that the slides are not well spread or well stained, or the bacterial suspensions do not show a sufficient number of bacteria—*i. e.*, two or three to a cell—to give results showing a minimum amount of variation. In other words, one must learn to discard at a glance certain preparations.

(*b*) With normal serums we have found well-marked variations in the phagocytic indices, no matter with what care the preparations have been made, selected, and counted. These results, however, with several normal serums agree within certain limits in a way which we have never been able to find for serums from tuberculous patients, the difference being that the degree

* The Practitioner, May, 1908.

of variation of the phagocytic indices with tuberculous serums is much more marked. Wright's idea of an opsonic index based upon the comparison of the phagocytic indices of two different serums has been strongly combated by some, the contention of his critics being that a normal opsonic index could not be defined. One can best define the normal opsonic index as the relation between the phagocytic indices of two or more supposedly normal and healthy individuals, and under the conditions with which one estimates these indices the results correspond fairly closely, provided the only condition varied be the change in serum, yet the relation is a variable one. What one means, therefore, by the normal opsonic index, which is to be compared to the index obtained with the serum from a tuberculous individual, is the variation noted in the results obtained by estimating phagocytic indices for individuals not invaded by a pathogenic microorganism.

With serum from tuberculous patients we have invariably found much more extreme degrees of variation than with normal serum, regardless of the single low or high opsonic index. If the index be estimated in units and tenths, as is usually done, and be charted according to the variations in units and tenths, it will be readily seen what one means by an extreme variation in readings for the tuberculous serum and by the limited variations for normal serum. It is true that with an invaded individual one may obtain by single estimations an extremely low index, such as is not found with the normal serum, yet we have never felt ourselves justified in concluding from such a reading that we were dealing with an infected individual, since such a single variation might be due to some error in technic. Yet we maintain that, when one secures, after repeated estimations, particularly when carried out at intervals of three or four days over a period of two or three weeks, a chart showing variations in the activity of the tuberculous serum which are not found with normal serum, this chart means that pathological changes have affected the blood.

At no time, we believe, can a single high or low index be relied upon for tuberculin therapy, and yet after repeated estimations it is possible that one might obtain more or less constant variations, which would be of use in giving inoculations.

3. Cases not under Tuberculin Therapy.—For comparison we have taken the charts obtained by recording the phagocytic indices of two normal healthy individuals, the estimations having been made by the different individuals with each one's own standard suspension and after one's own technic, and these normal serums (four specimens) were carried through with several (four to sixteen) other specimens numbered blindly, in order to avoid error due to expectancy. At times we employed methods of pooling four normal serums and recording estimations of these normals by four individuals,

and we could not see that greater accuracy was obtained thereby (Charts 1 and 2).

The charts (1 and 2) for the two normal individuals correspond fairly closely and show variations somewhat larger than obtained by Wright and many others, yet it is striking that there appear no such low and high figures as are found for the tuberculous.

A. Certain tuberculous cases were never given tuberculin, and the indices were estimated at intervals of twenty-four hours for seven days, at intervals of three and four days, at intervals of ten to fourteen days (Charts 3 and 8).

Among fourteen pulmonary cases examined, two gave indices within normal limits, and two within wide variations, and this fact called our attention to the inconstant occurrence of a low index in tuberculous infections (Charts 3 to 6).

If one studies Charts 3 and 4, it is evident that the index is at first normal in two pulmonary cases who would not tolerate without reactions injections of $\frac{1}{10000}$ milligram of the bacillen emulsion. Case with Chart 3 was advanced (Turban III, condition poor), with involvement of the entire right lower and the anterior upper portion of the upper right lobe and the anterior upper portion of the left upper lobe, and with a sinus from operation done two months previously for a left empyema. This patient lived only a few weeks after the last record was made. The second patient has improved slowly under good hygienic treatment.

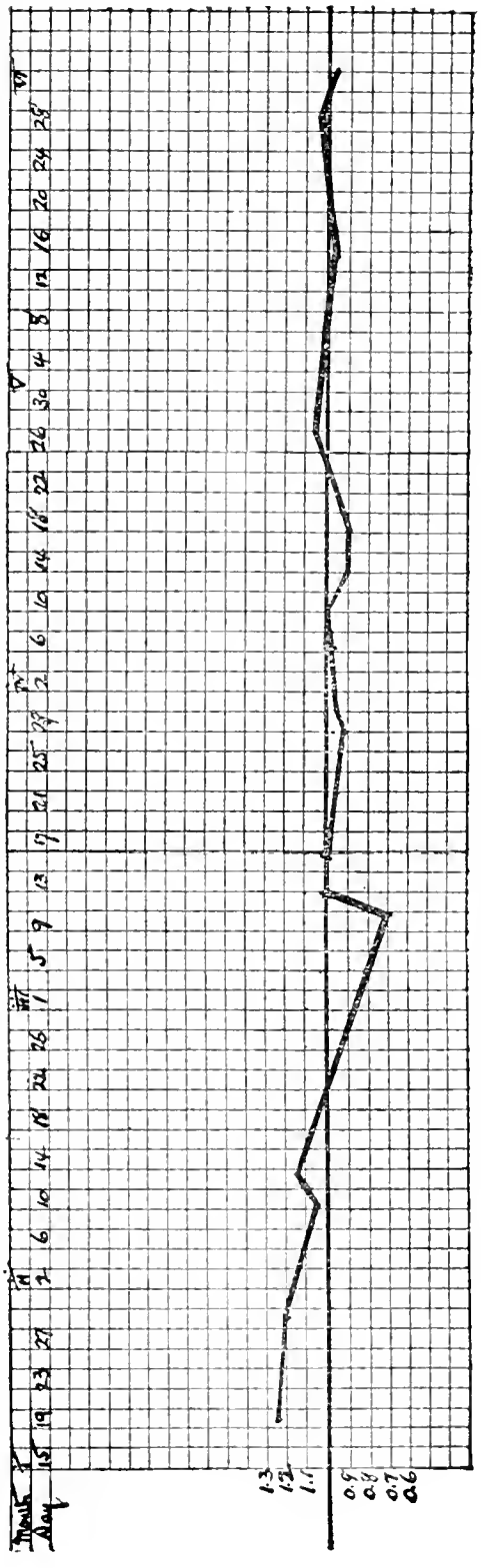
In ten pulmonary cases the few isolated determinations of the index were low—below 0.6, regardless of condition.

The indices, therefore, did not correspond to the clinical condition, and they certainly were not to be used as guides for inoculation.

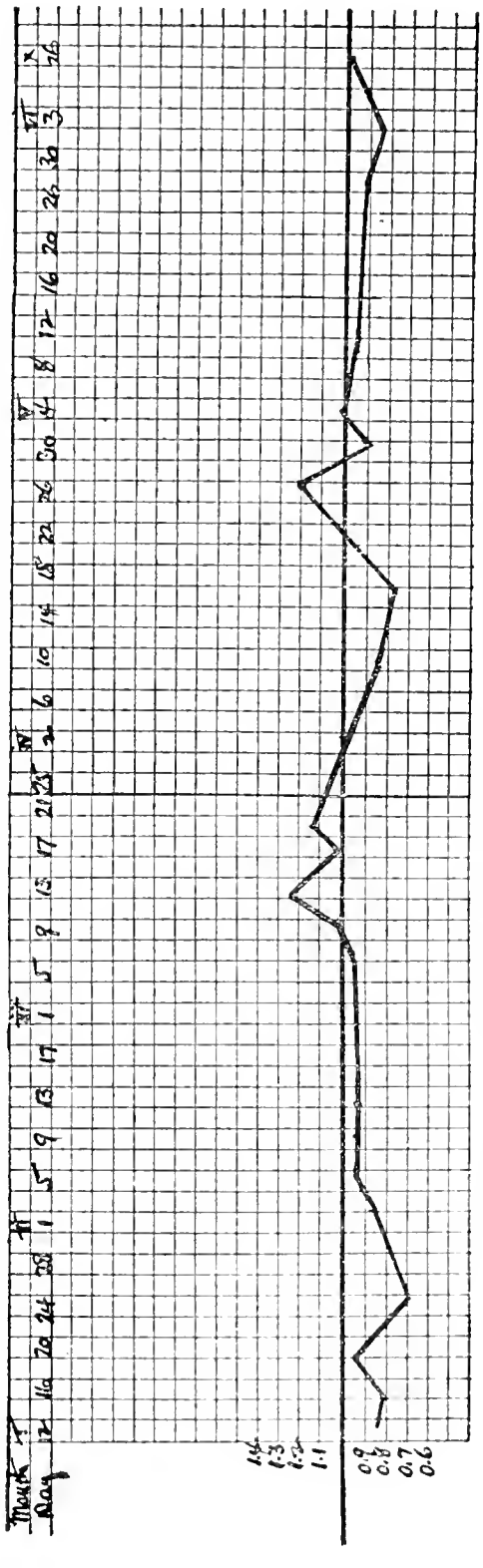
From the nature of the tubercle bacillus infection (chronicity), and from the relation of opsonin to infection, one is justified in applying studies of the opsonic index in non-pulmonary conditions to the problems relating to pulmonary invasion. After a few observations upon pulmonary cases it was not considered advisable, for obvious reasons, to keep such patients confined to hospital wards in the city or to insist upon two or three visits a week to the dispensary and laboratory for long periods; therefore, our results are based mainly upon the study of non-pulmonary cases and inactive pulmonary cases with lesions in other tissues and organs.

B. In this set the cases were of non-tuberculous infection in a supposedly non-tuberculous individual, and the indices over a long period of time were determined in order to show any variations in a tuberculo-opsonic index due to a non-tuberculous infection (Charts 9, 10).

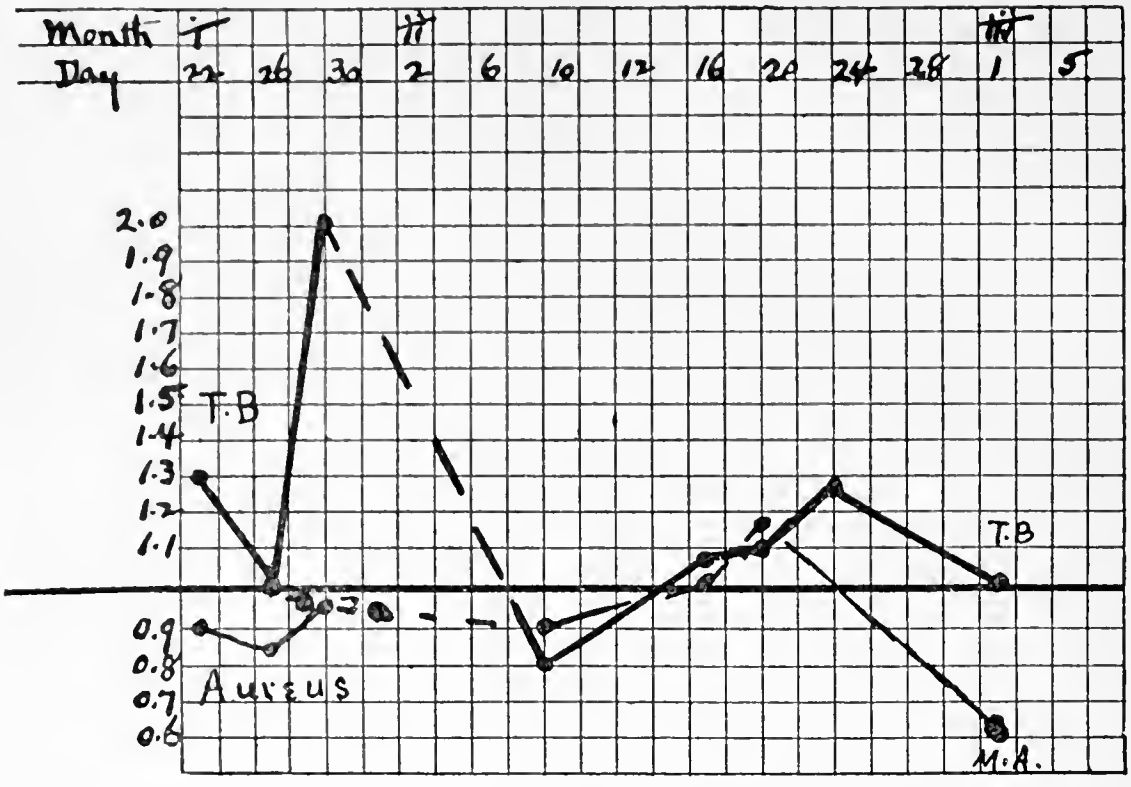
From the charts of cases of non-tuberculous infection we do not draw conclusions, since no one of them (Charts 9, 10) was studied a considerable length of time, and we have not confirmed the wide variations in the index



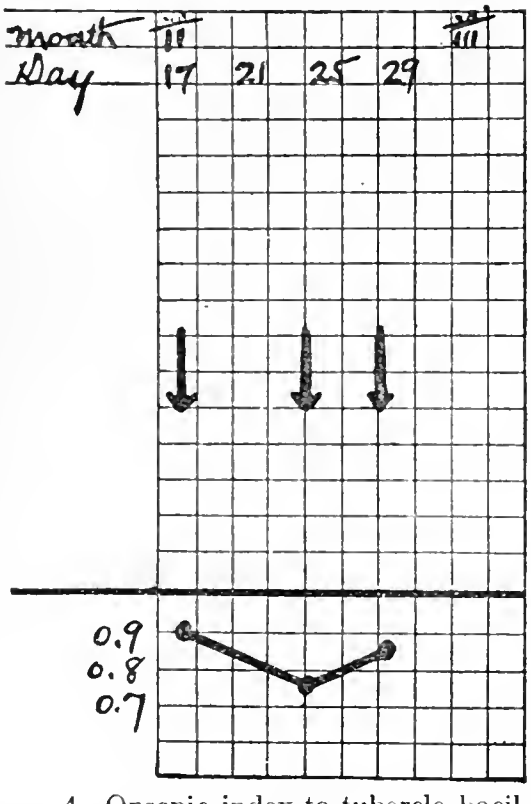
1. Opsonic index to tubercle bacillus. Healthy man. Control.



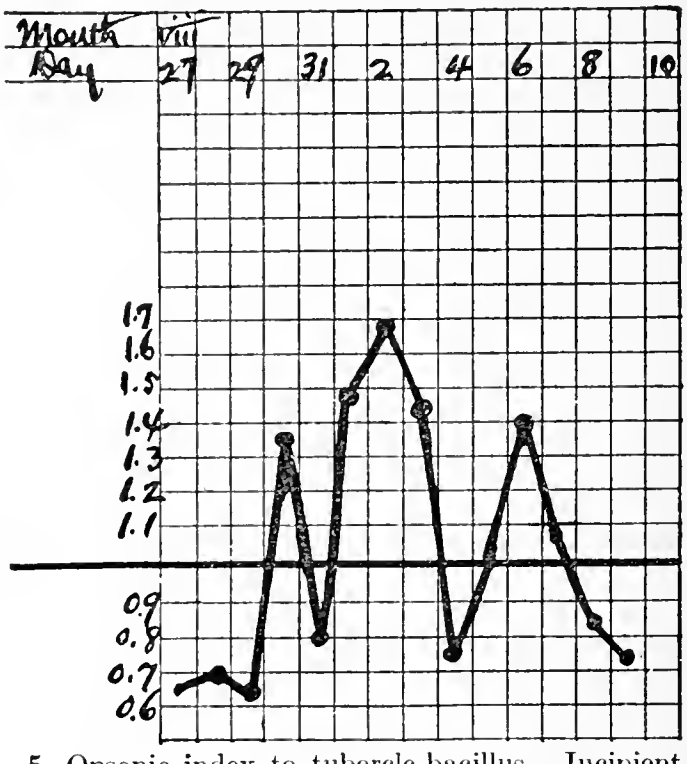
2. Opsonic index to tubercle bacillus. Healthy man. Control.



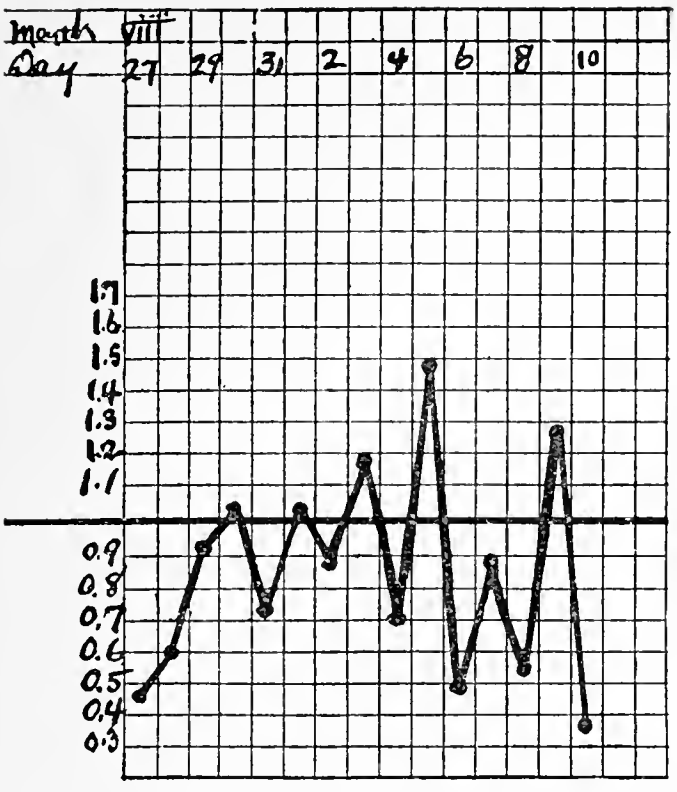
3. Opsonic index to tubercle bacillus and to Micrococcus aureus. Tubercle bacilli above. Micrococcus aureus below.
Pulmonary tuberculosis; both apices; dyspnea; asthenia.



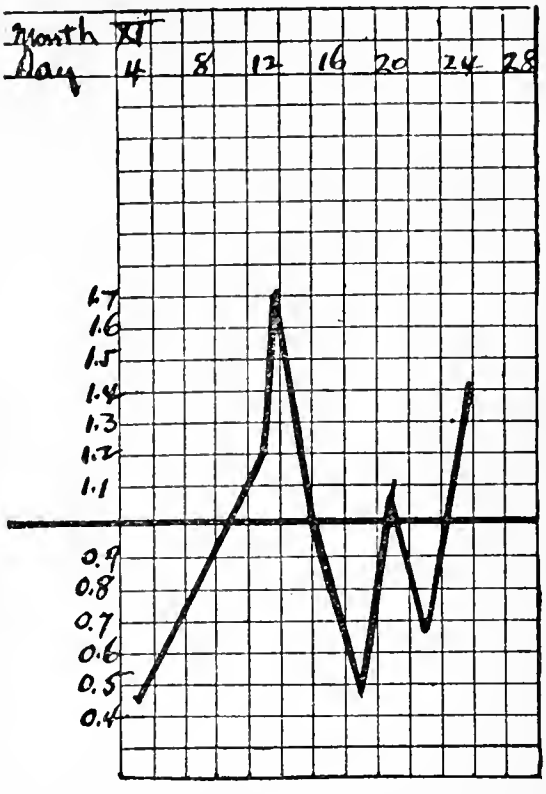
4. Opsonic index to tubercle bacillus. Case of pulmonary tuberculosis with cervical adenitis.



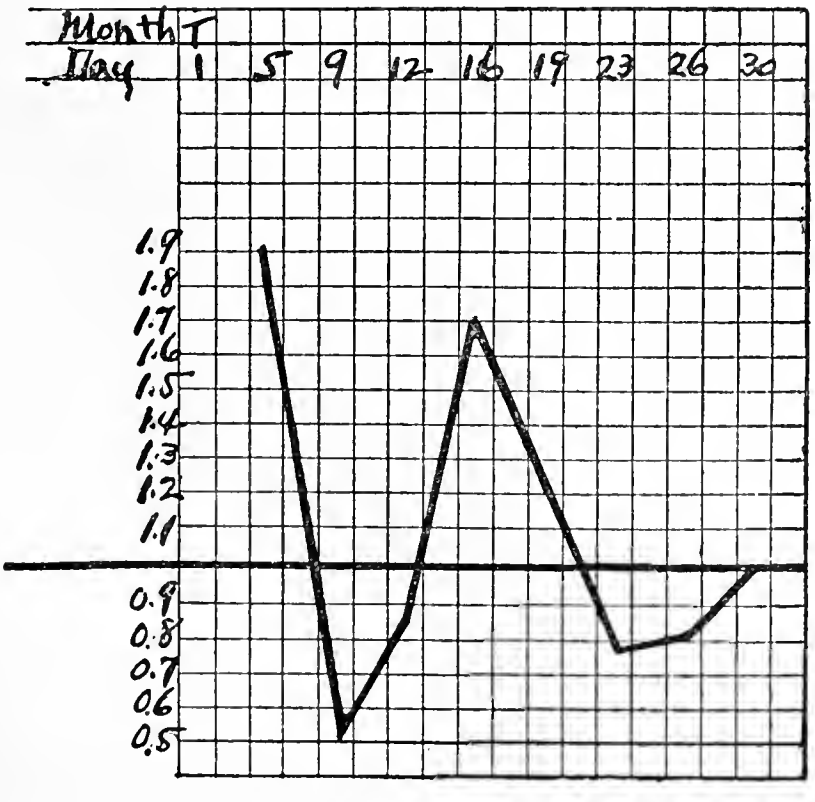
5. Opsonic index to tubercle bacillus. Incipient pulmonary tuberculosis.



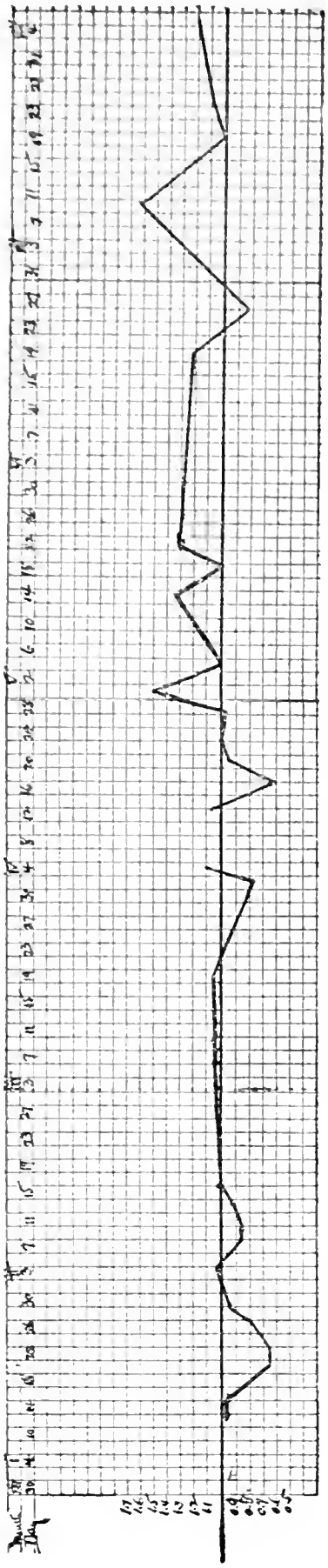
6. Opsonic index to tubercle bacillus. Case of advanced pulmonary tuberculosis.



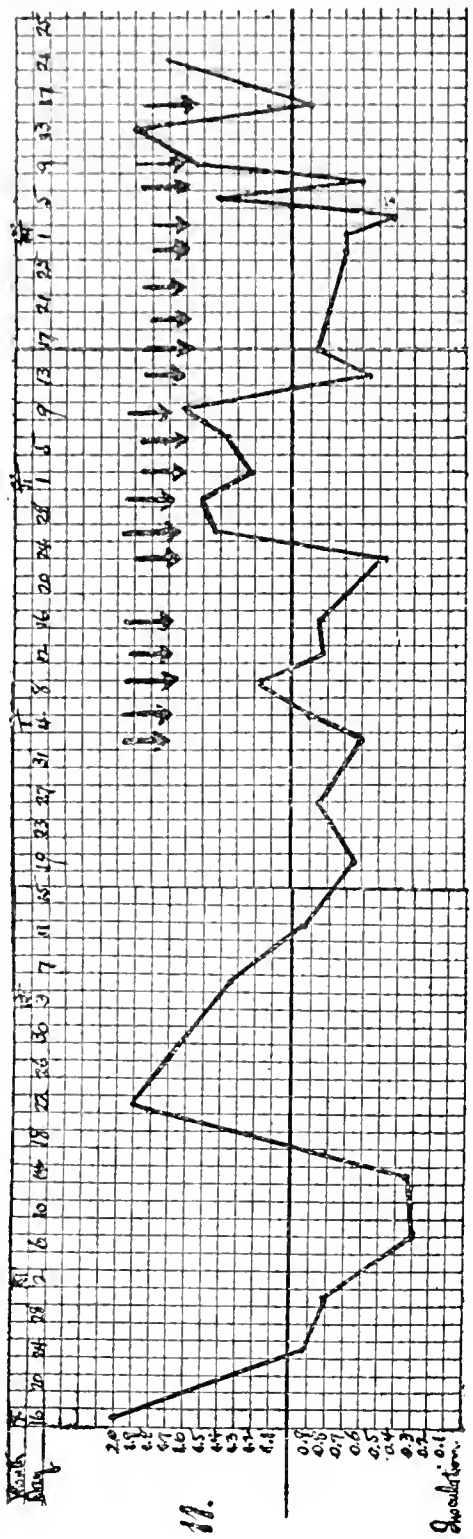
7. Opsonic index to tubercle bacillus. Tuberculosis of bone.



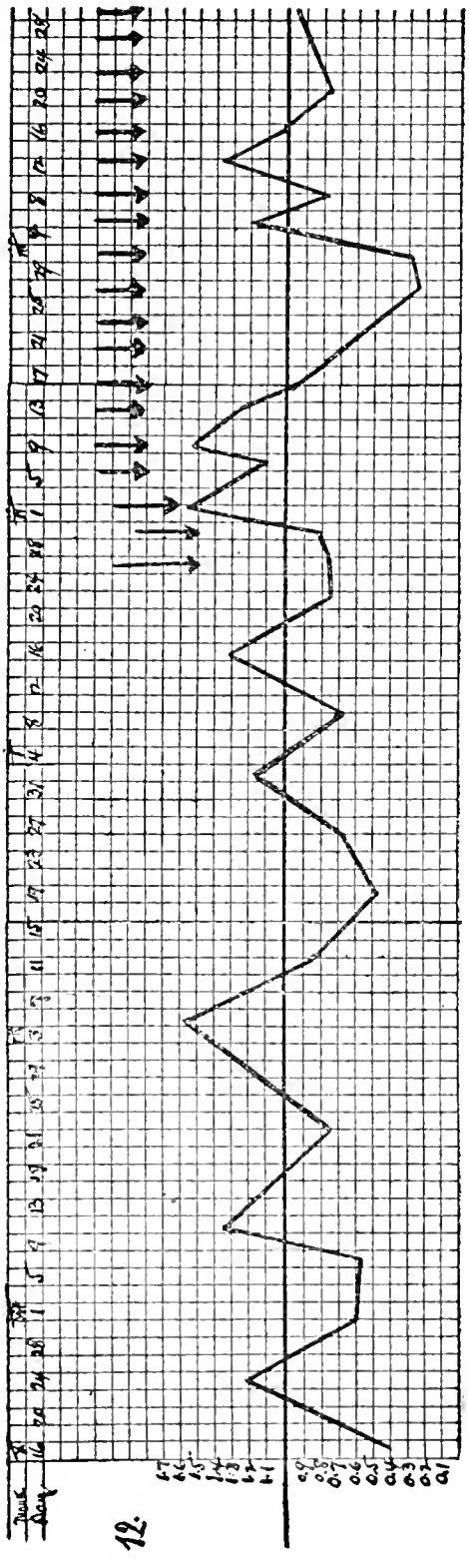
8. Opsonic index to tubercle bacillus. Tuberculosis of bone.



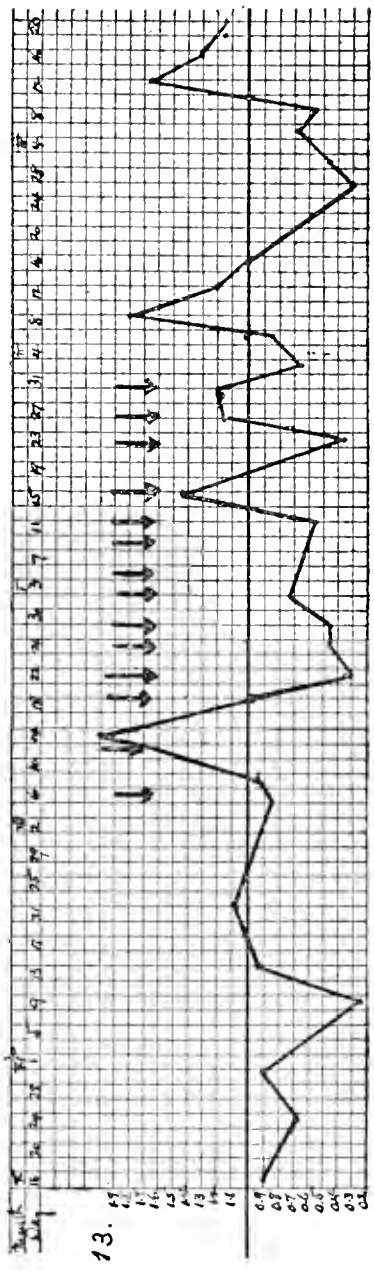
9. Opsonic index to tubercle bacillus. Empyema.



11. Opsonic index to tubercle bacillus. Bone tuberculosis. Inoculations.



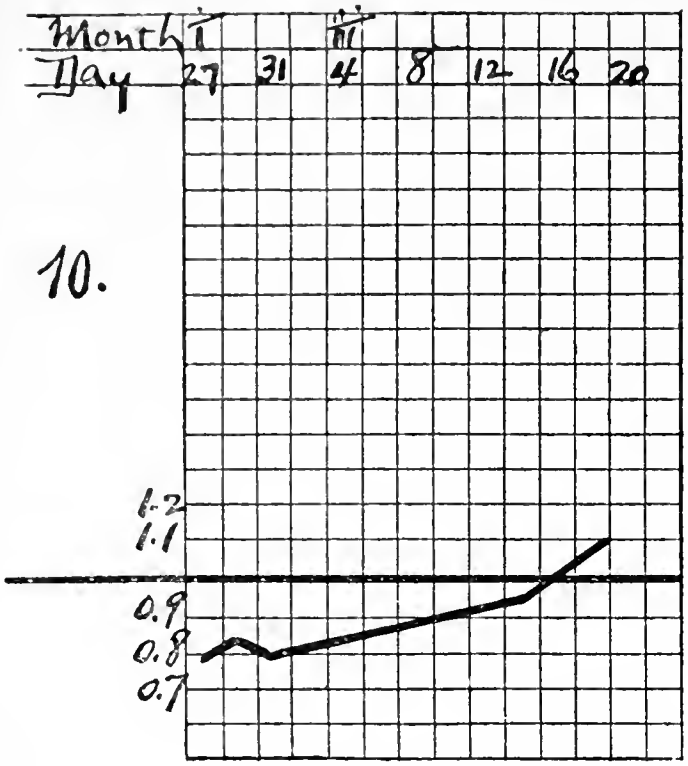
12. Opsonic index to tubercle bacillus. Bone tuberculosis.



13. Opsonic index to tubercle bacillus. Bone tuberculosis.

noted at certain periods. As a rule, it seems to us that we may obtain low readings in non-tuberculous infections, but not the degree of variation noted in tuberculous conditions.

4. Cases under Tuberculin Therapy.—C. With other tuberculous cases an index curve was established before inoculations in order to determine the influence of tuberculin upon the index, the intervals between index determinations being kept the same (Charts 11 to 14). These records also served for comparison with records from set A, and in one instance daily estimations for seven days were made for comparison with similar estimations in set A.



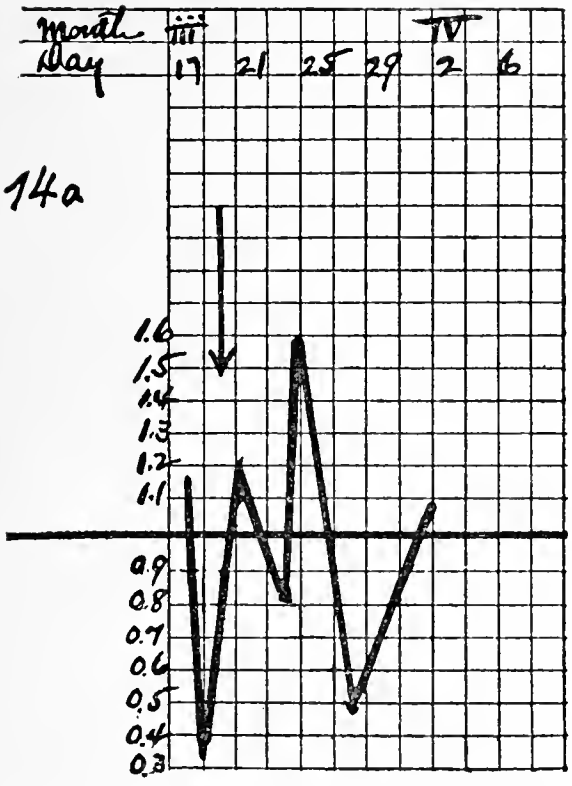
10. Opsonic index to tubercle bacillus. Pneumococcus. Septic knee.

Under set C records were made after inoculations with widely varying doses of tuberculin. The tuberculin used was Saranac Laboratory bacillen emulsion No. 11, and Koch's bacillen emulsion, and the doses were progressively increased, as recommended by Trudeau.

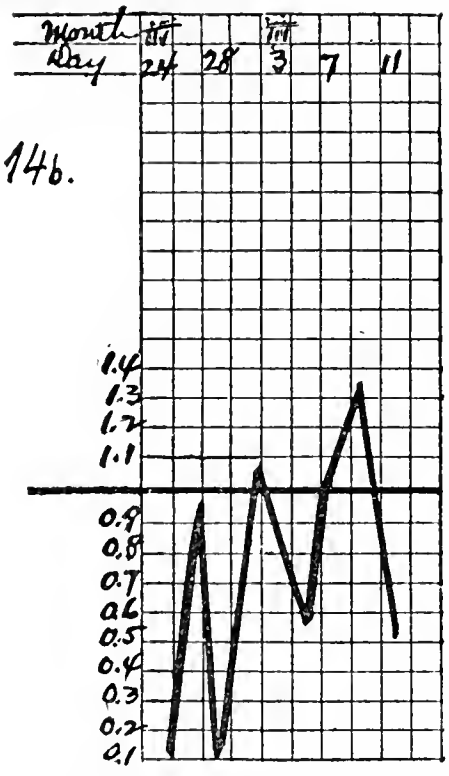
Seven charts (14a to 14g), setting forth the daily variation after a single dose, show the same inconstancy noted in the longer records. We have repeatedly obtained the same results, each chart showing what may be considered a negative phase, but with marked differences following, probably due to the impossibility of preventing an effect by the tuberculous individual's change in opsonin upon the curve which would have been produced by the inoculation alone.

We are justified in this statement by a study of the Charts in sets A and B.

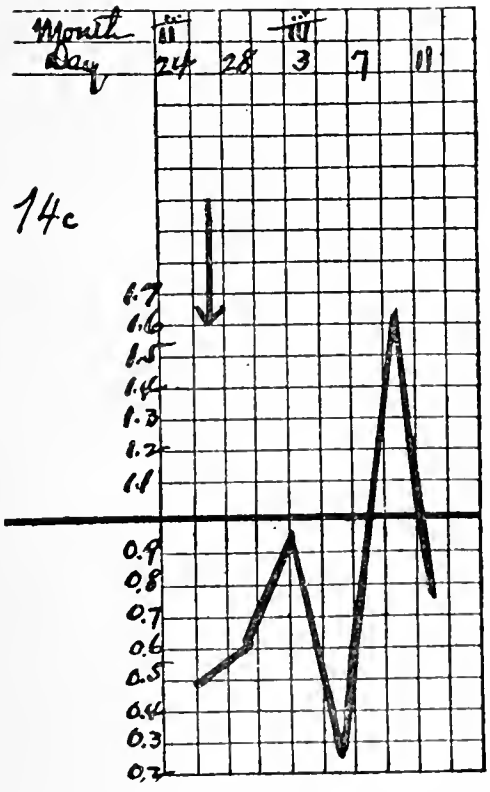
The charts from cases under tuberculin therapy (sets C and D) show an extremely inconstant variation, not only before, but also after, inoculations were begun. In a few instances (type Chart 13) the general character of the curve seemed to change, the average index being higher and at the same time less steady. After several months the result of inoculation, judging from some charts, was the steadying of the index with the mean



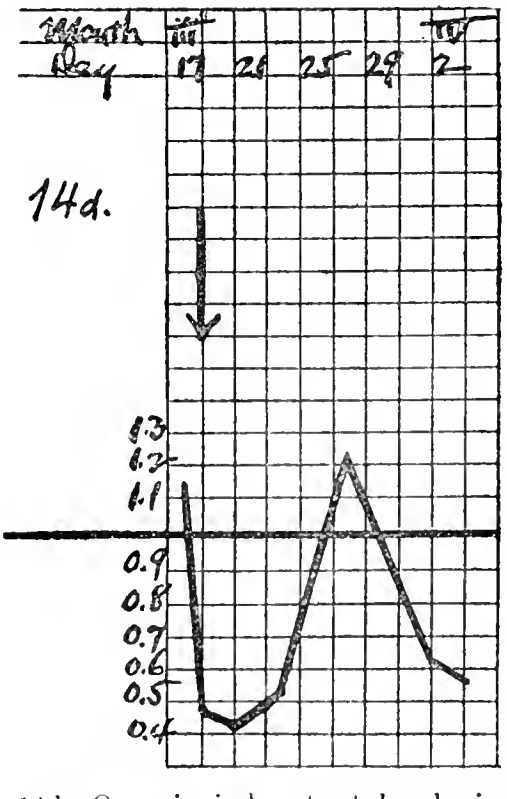
14a. Opsonic index to tubercle bacillus. Tuberculosis of bone. After single dose of 0.0006⅔ mg., subsequent to sixteen doses.



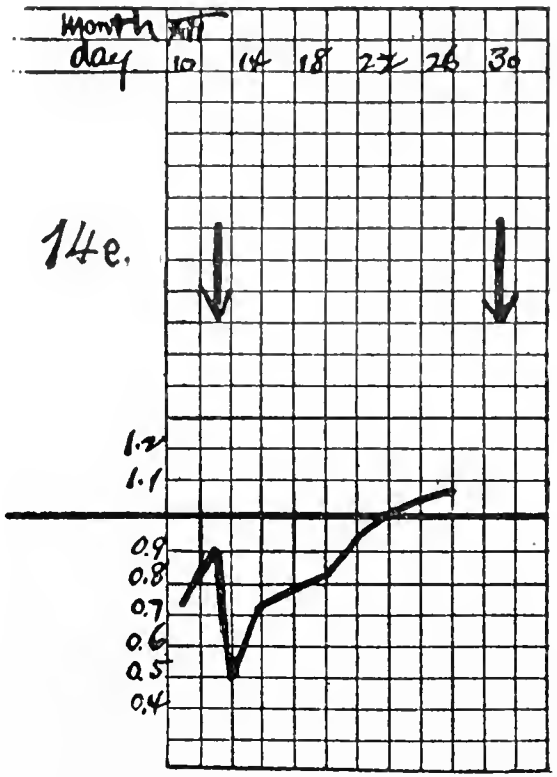
14b. Opsonic index to tubercle bacillus. Tuberculosis of bone. Inoculations from December 15, 1907, to February 17, 1908. No inoculations after repetition of small dose.



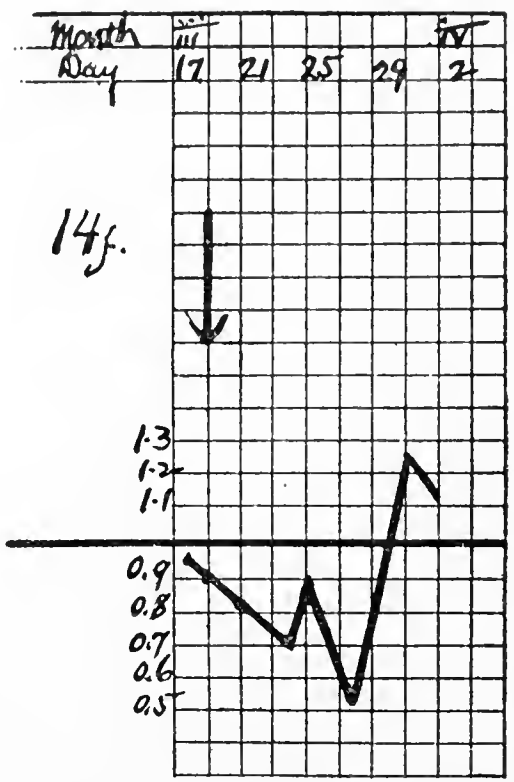
14c. Opsonic index to tubercle bacillus. After single dose of 0.0006 mg., after sixteen repetitions of same dose.



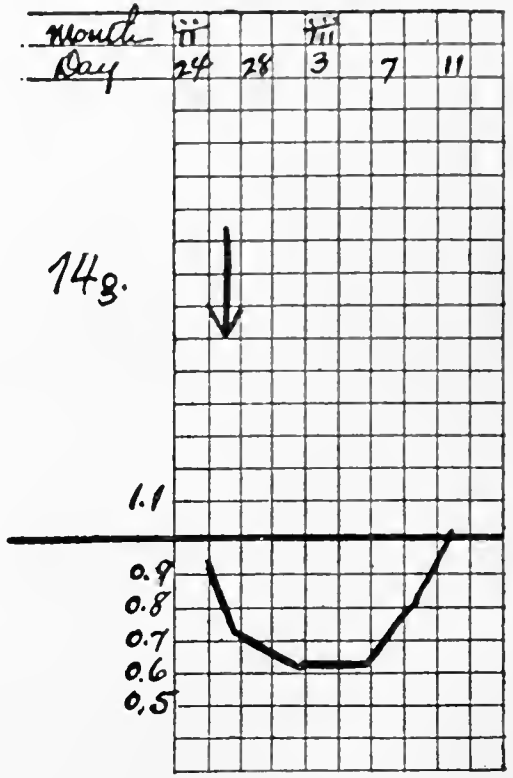
14d. Opsonic index to tubercle index. Bone tuberculosis. After a single dose of 0.001 mg., subsequent to increasing doses.



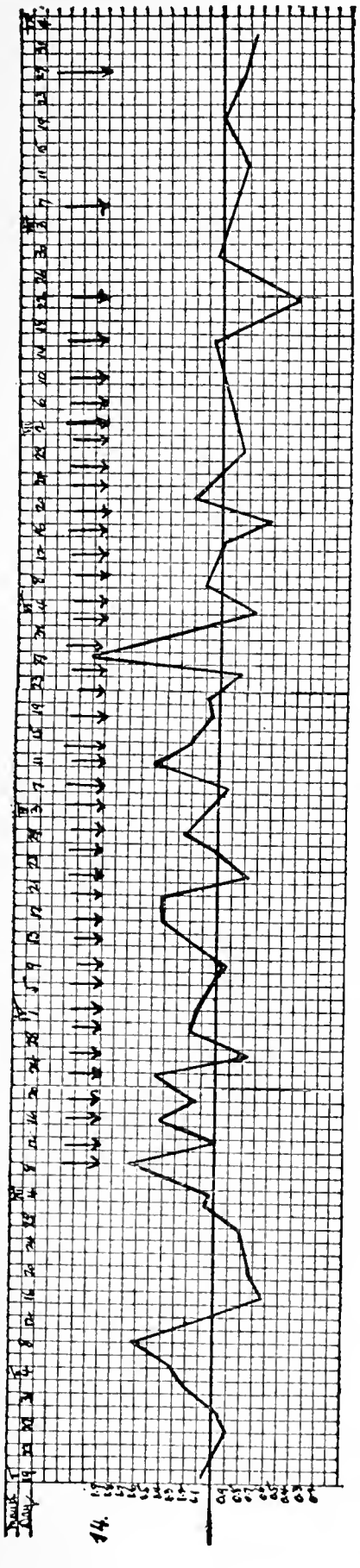
14e. Opsonic index. Effect of single dose of 0.03⅓ mg., after increasing doses to 0.03 mg.



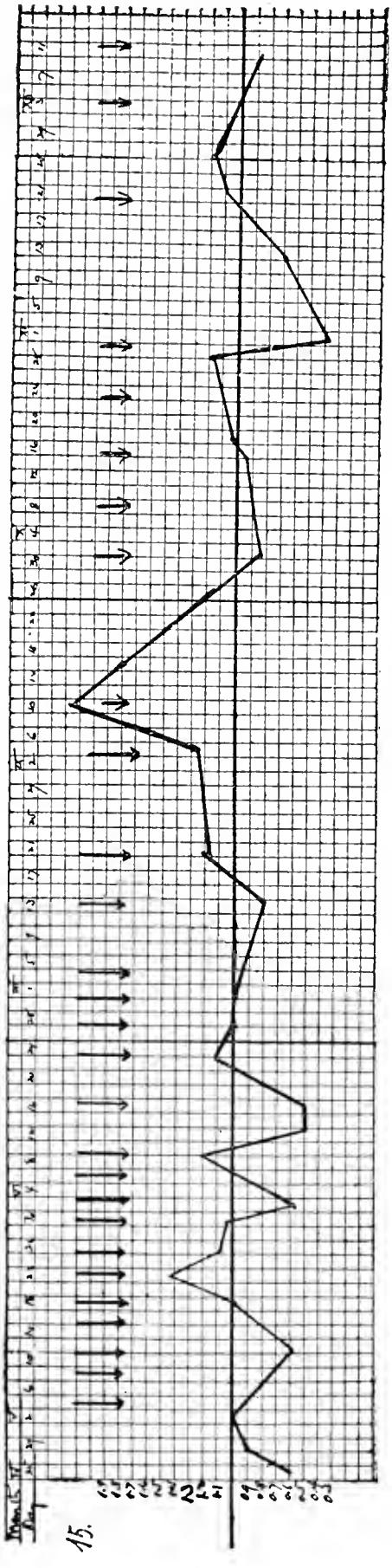
14f. Opsonic index to tubercle bacillus. Effect of single dose 0.03⅓ mg., after increasing doses to 0.03 mg.



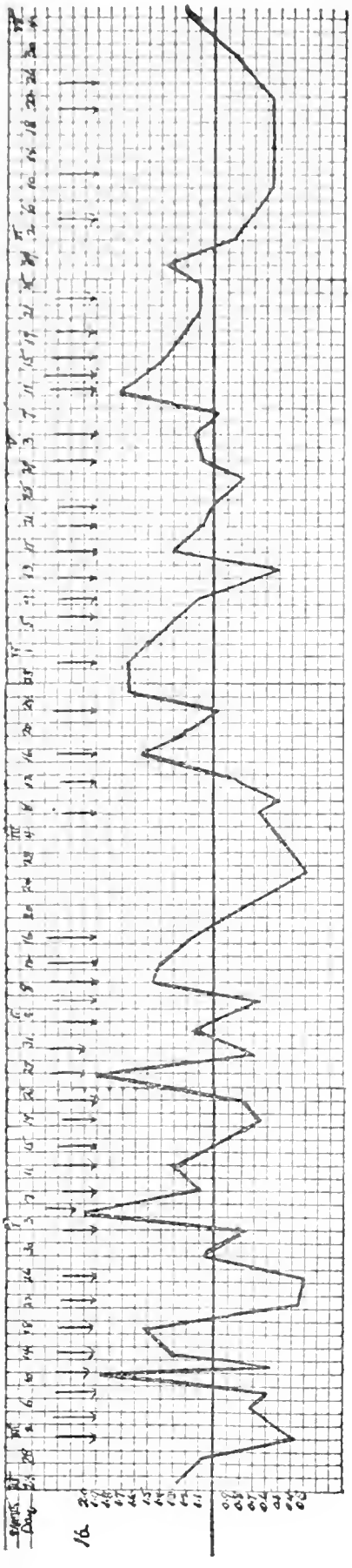
14g. Opsonic index to tubercle bacillus. After single dose of 0.0003⅓ mg., after sixteen repetitions of same dose.



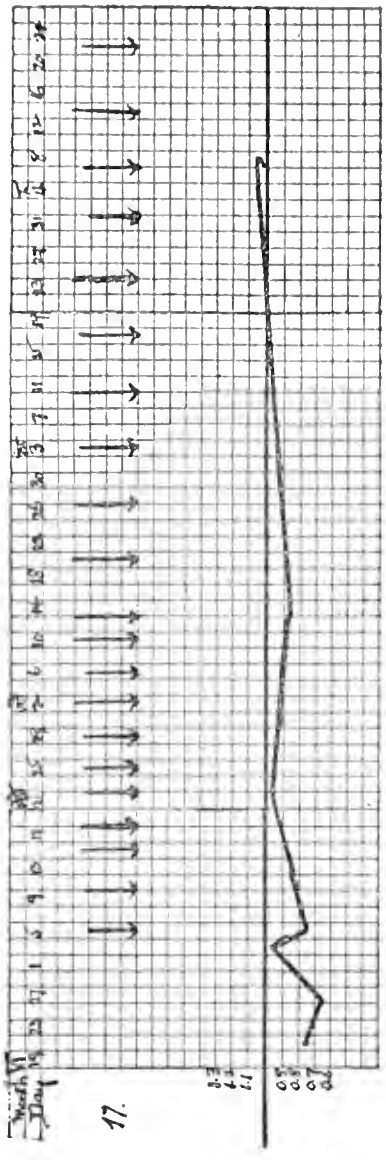
14. Opsonic index to tubercle bacillus. Cervical adenitis, tubercular.



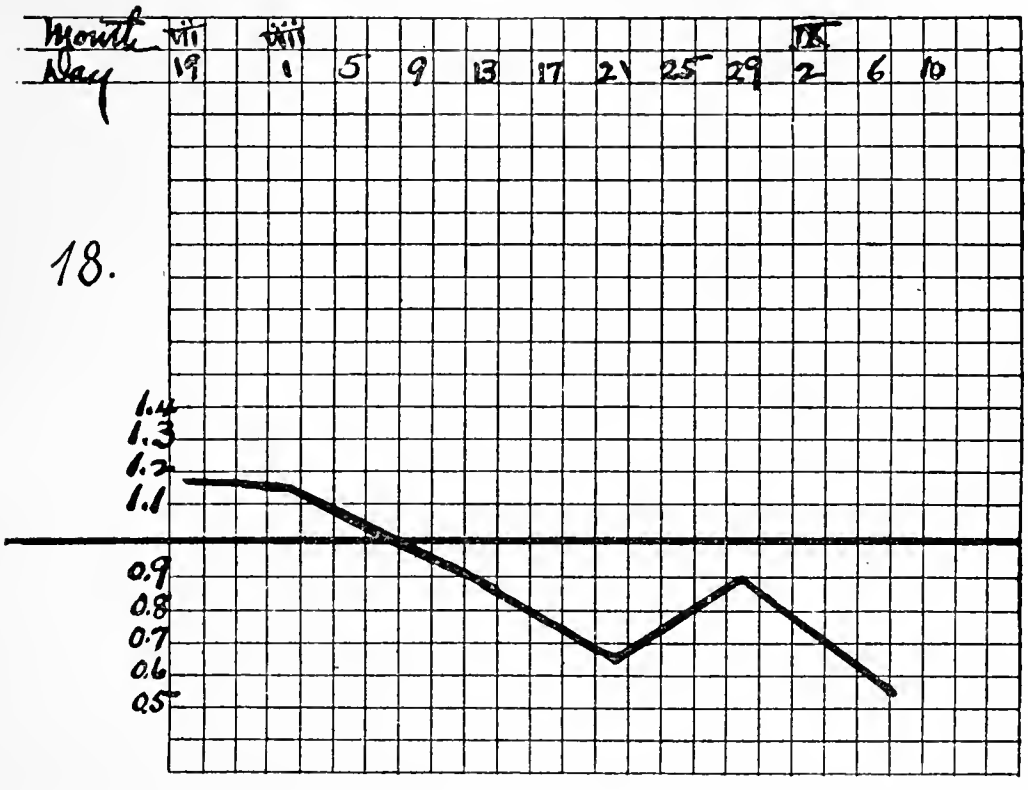
15. Opsonic index to tubercle bacillus. Tuberculous cervical adenitis. Phlyctenular conjunctivitis.



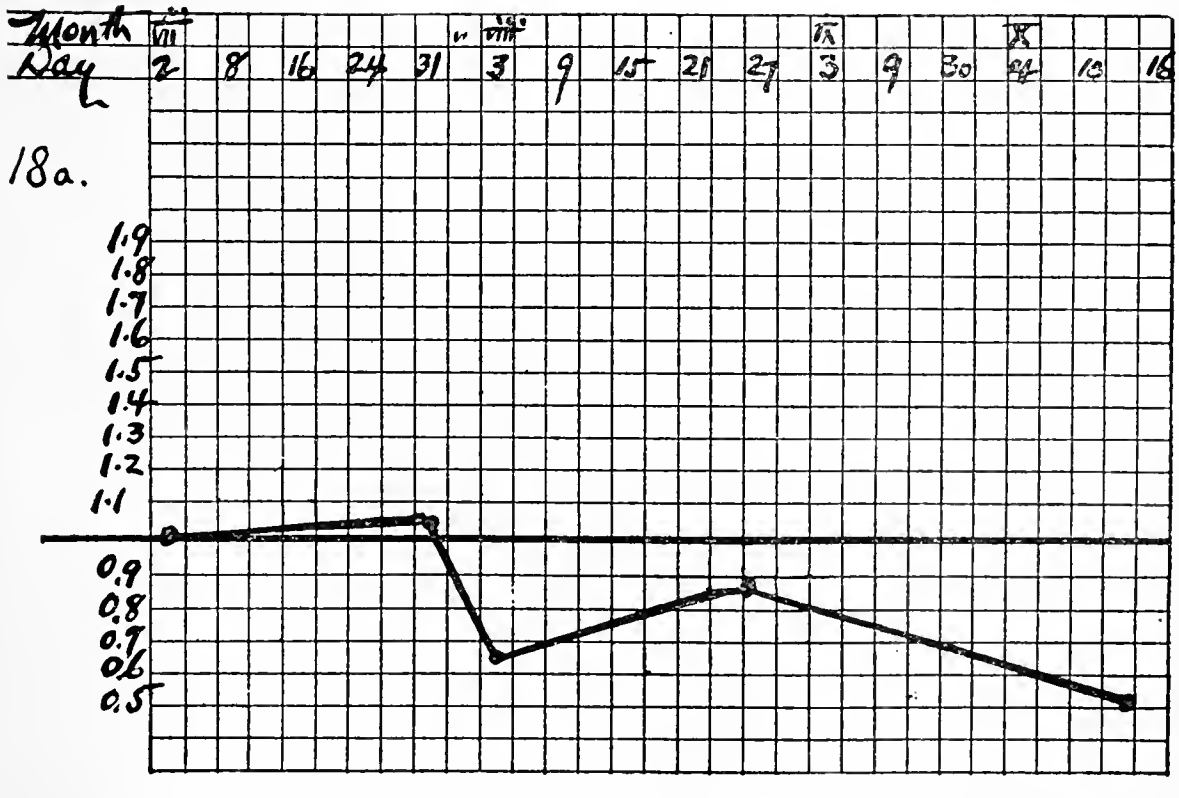
16. Opsonic index to tubercle bacillus. Tuberculous cervical adenitis.



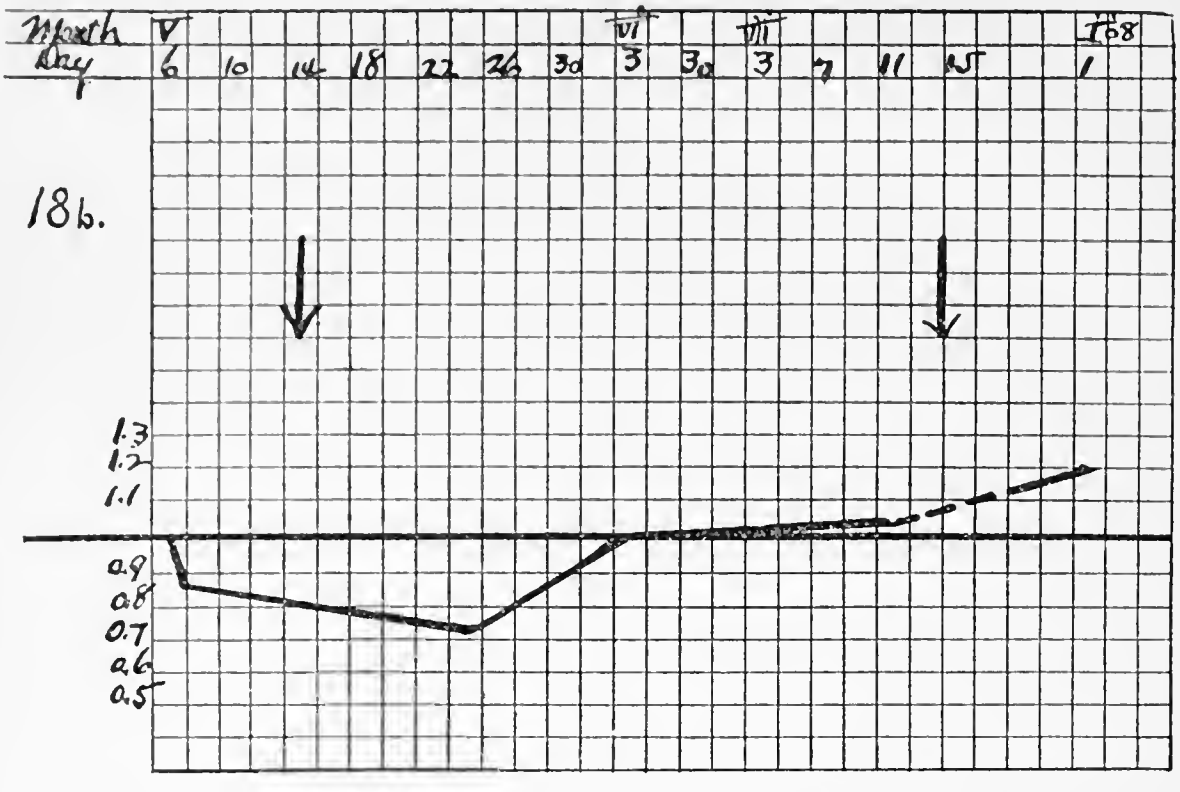
17. Opsonic index to tubercle bacillus. Tuberculous glands in groin. Pott's disease. Psoas abscess.



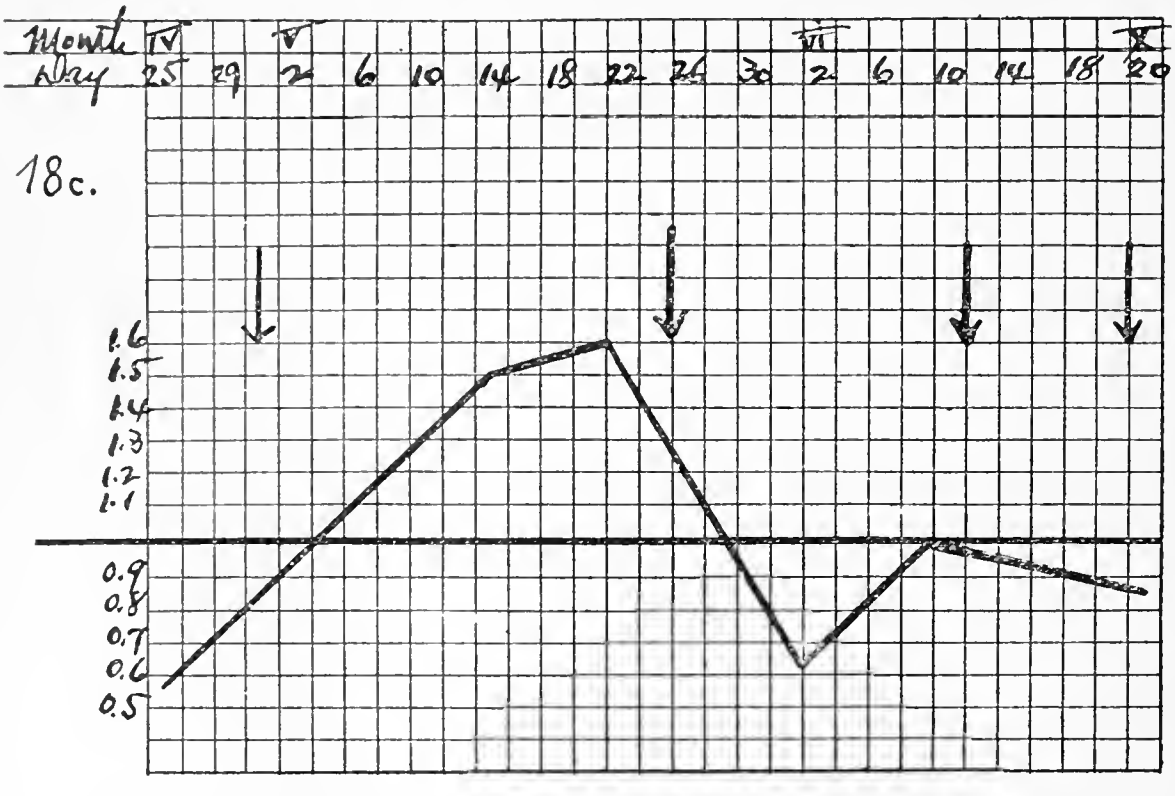
18. Opsonic index to tubercle bacillus. Tuberculosis of kidney and bladder.



18a. Opsonic index to tubercle bacillus. Tuberculosis of bone.



18b. Opsonic index to tubercle bacillus. Tuberculosis of kidney, bladder, and prostate.

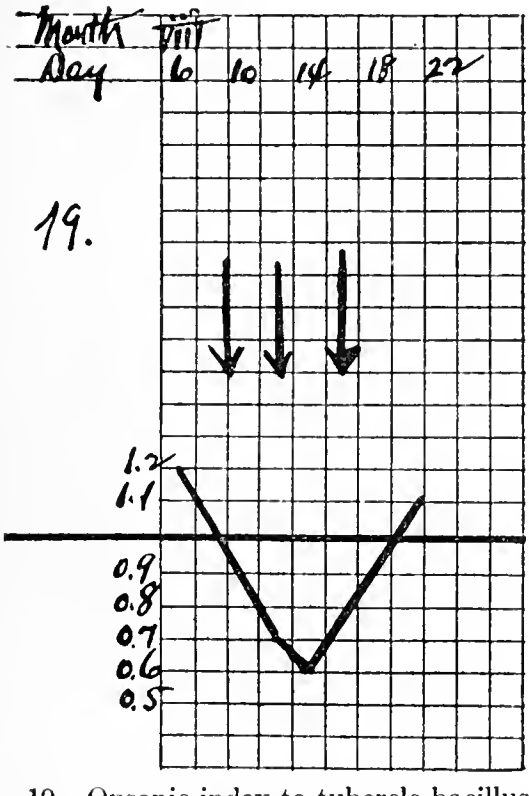


18c. Opsonic index to tubercle bacillus. Tuberculosis of cervical glands.

approaching normal, but such an apparently desirable change occurred in 2 only out of 10 cases.

D. A fourth set of cases were given tuberculin according to Denys' and Sahli's method, as modified by Trudeau and used at Saranac Lake, and no systematic estimation, but occasional determination of the opsonic index, was made to find the relation between clinical condition and the index (Charts 15 to 18).

If one considered alone the Charts 15 to 18, one might conclude that the index is markedly influenced by the inoculation of tuberculin. But when compared to sets A and C, it is evident that the same variations will occur in a tuberculous individual without inoculation. And, further, Charts 18, 18a, 18b, 18c, indicate that an index may gradually decrease in value as a patient improves and apparently recovers (Chart 18).



19. Opsonic index to tubercle bacillus. Normal individual.

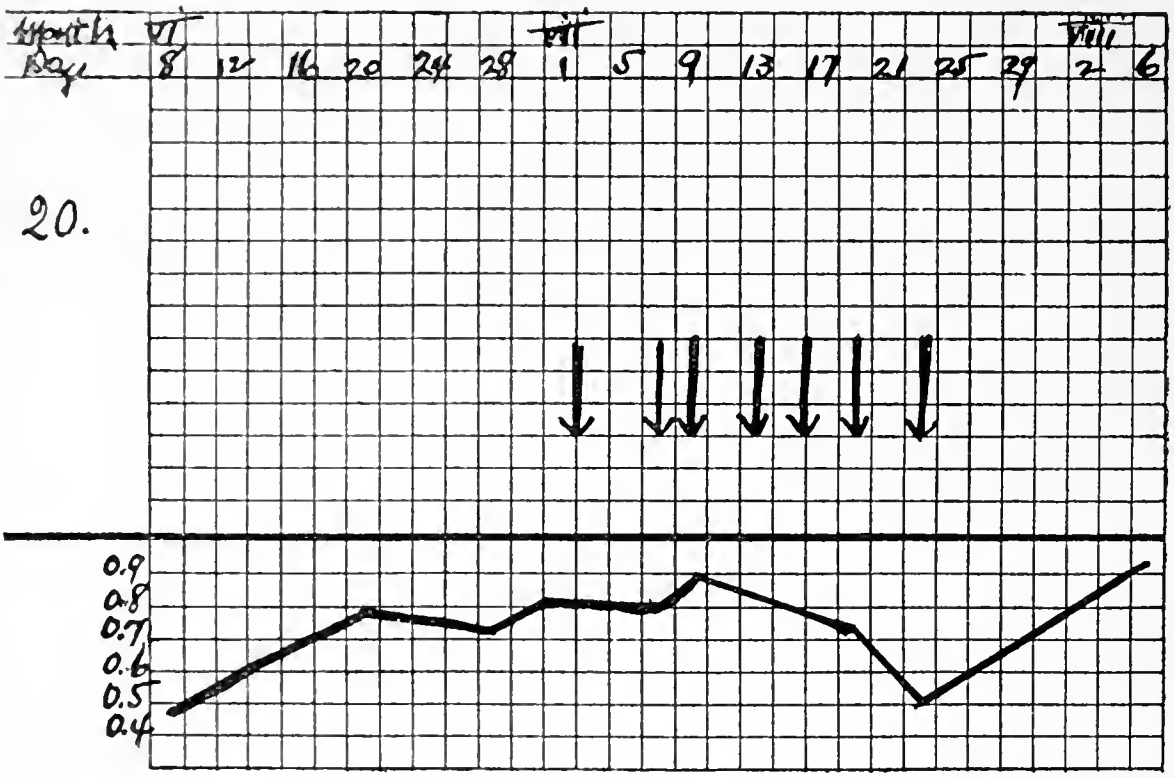
Finally, one non-tuberculous individual accepted a few inoculations in order to determine the influence upon a normal index, and two cases of Hodgkin's disease and one of non-tuberculous cervical adenitis were given tuberculin after recording persistent low indices, which, according to Wright, suggested a tuberculous infection, not necessarily in the enlarged glands. Tuberculin infections raised the index, but no beneficial effect was noted (Charts 19 to 22).

The few observations upon a single individual after injections of varying doses of tuberculin do not permit one to lay stress upon conclusions from such a record, but the charts from the three cases of non-tuberculous lymph-node disease are worth noting. In a case of Hodgkin's disease (Chart 20) with a gland hyperplasia showing structure suggesting an endothelioma, tuberculin inoculations produced no change, and judging from Chart 19 it is possible that had the dosage been larger, the character of the curve would have been altered. Chart 21, from a typical case of Hodgkin's, gives evidence of a general raising of the index after inoculations, and this occurred with no improvement in the clinical condition.

The case of non-tuberculous infective adenitis (Chart 22), for which we

at first accepted a diagnosis of tuberculous adenitis, has not responded to repeated tuberculin tests over a period of two years, during which time she has taken two series of tuberculin inoculations. The effect on the index is to be noted by studying Chart 22.

From these results we have drawn the conclusions that: Very high indices are more suggestive of infection than the low if one may judge from Charts 20 and 21, in which the persistently low readings—indicating lowered resistance—were raised by inoculations, although we could not prove the cases tuberculous.

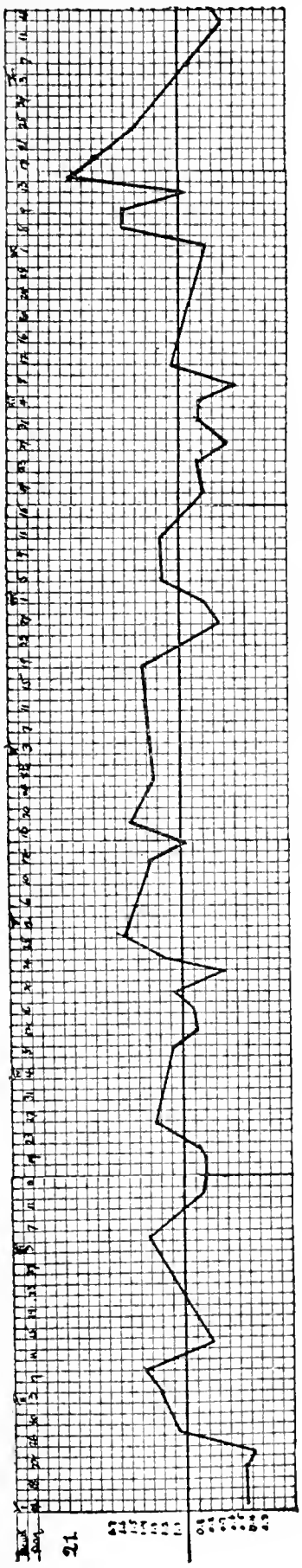


20. Opsonic index to tubercle bacillus. Hodgkin's disease.

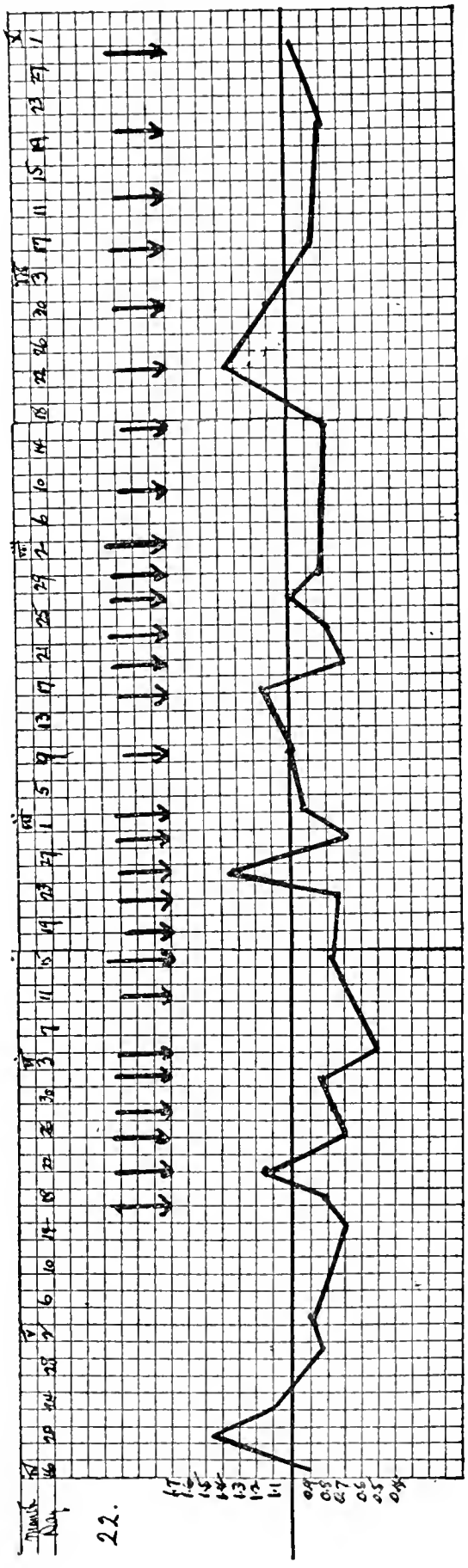
The one fact emphasized by all the records is that wide variations in the index occur in tuberculous individuals, but not invariably over short periods of time, so that to establish a pathological variation the safe plan is to estimate indices two or three times a week for a period of two weeks.

While the variations are sufficiently great to mark a serum as abnormal and perhaps pathological, yet they are so wide without inoculations and so inconstant after inoculations that one cannot safely use the index as a guide for tuberculin inoculations.

Nevertheless, in studying a number of cases not pulmonary the conclusion seems to be justified that persistently low indices, while giving tuberculin, call for discontinuance of inoculations, and yet one will be able to judge



21. Opsonic index to tubercle bacillus. Hodgkin's disease.



22. Opsonic index to tubercle bacillus. Tuberculous cervical adenitis.

from clinical symptoms before the persistently low index has been established. From a single low index one can draw no conclusions, a statement justified by the charts from untreated cases.

The author extends to Dr. Warren and Dr. Hoobler, of the laboratory staff, his sincerest thanks for their invaluable assistance during the work and in preparing the charts.

REFERENCES.

North: New York Medical Journal, 1907, p. 1148.
North: Referred to by Park and Biggs, p. 80.
Park and Biggs: Jour. Medical Research, 1907, xvii, 77–88.
Reyn and Kjer-Petersen: Lancet, 1908, vol. i, 919, 1000.
Trudeau: American Journal Medical Sciences, 1906, vol. cxxxii, p. 175.
Smith, Radcliffe, Elder, and Crossley: Lancet, July 18, 1908, vol. ii, p. 148. (The article in the Lancet by Smith, Radcliffe, Elder, and Crossley appeared after this paper had been completed. The charts obtained by them are similar to those in this text.)

L'index opsonique dans certaines infections tuberculeuses.—(HASTINGS.)

1. Possibilité d'estimer l'index opsonique.

2. Index opsonique normal et variations trouvées avec les sérums normaux. Variations trouvées avec les sérums d'individus tuberculeux.

3. Variations trouvées dans l'index opsonique d'individus qui n'ont pas été soumis à la thérapie de la tuberculine.

4. Variations de l'index opsonique dans les cas soumis au traitement par la tuberculine.

A juger d'après la nature de l'infection tuberculeuse (chronique) et de la relation de l'opsonine à l'infection, on peut appliquer aux problèmes concernant la tuberculose pulmonaire, les études faites sur l'index opsonique de la tuberculose non-pulmonaire.

Sur douze cas pulmonaires, deux seulement ont donné des indices restant dans les limites normales et c'est ce fait qui a attiré notre attention sur l'inconstance d'un index opsonique inférieur se trouvant dans les infections tuberculeuses.

Dans dix cas pulmonaires, les quelques déterminations isolées de l'index qui ont été faites, montraient un degré inférieur, sous 0.6, l'état du malade n'ayant pas été considéré.

Les indices ne correspondaient pas donc à l'état clinique et on ne devait certainement pas les employer comme guides dans l'inoculation.

Le fait sur lequel tous les rapports accentuent est, qu'on voit de larges variations dans l'index des individus tuberculeux, mais pas d'une manière invariable quand il s'agit de courtes durées; par conséquent, le meilleur

plan pour établir une variation pathologique, est d'estimer les indices deux ou trois fois par semaine pendant quinze jours.

Bien que les variations soient assez grandes pour qu'on puisse considérer un sérum comme anormal et peut-être comme pathologique; elles sont si larges quand on ne fait pas d'inoculations, et si inconstantes après les inoculations, qu'on ne peut pas employer l'index comme un guide sûr dans les inoculations de tuberculine.

Der opsonische Index in gewissen tuberkulösen Infektionen.— (HASTINGS.)

1. Die Möglichkeit, einen opsonischen Index abzuschätzen.
2. Der normale opsonische Index und die Variationen gefunden mit normalem Serum. Die Variationen mit dem Serum von tuberkulösen Individuen.
3. Variationen in dem opsonischen Index in Individuen, die nicht unter Tuberkulinbehandlung sind.
4. Variationen in dem opsonischen Index in Fällen unter Tuberkulinbehandlung.

Von der Natur des Tuberkelbacillus (Chronicität), und von der Beziehung des Opsonins zur Infektion ist man gerechtfertigt, die Forschungen über den opsonischen Index in non-pulmonären Zuständen auf die Probleme, die sich auf Lungentuberkulose beziehen, anzuwenden.

Von zwölf untersuchten Lungenfällen gaben zwei Indexe innerhalb normaler Grenzen, und diese Tatsache lenkte unsere Aufmerksamkeit auf das nicht konstante Vorkommen eines niederen Index in tuberkulösen Infektionen.

In zehn Lungenfällen waren die wenigen isolierten Indexbestimmungen niedrig, unter 0.6, ohne Rücksicht auf den Zustand.

Die Indexe stimmten deshalb nicht mit den klinischen Zuständen ein, und sie waren sicher nicht als ein Führer zur Inokulation zu benützen.

Die in allen Berichten hervorgehobene Tatsache ist, dass weite Schwankungen in dem Index bei Tuberkulösen vorkommen, aber nicht unveränderlich während kurzer Zeitperioden, so dass, um eine pathologische Variation festzustellen, der sichere Plan ist, die Indexe zwei- oder dreimal in einer Woche in einer Periode von zwei Wochen abzuschätzen.

Während die Variationen genügend gross sind, um ein Serum als abnorm und vielleicht pathologisch zu bezeichnen, sind dieselben ohne Impfungen so verschieden und nach Impfungen so inkonstant, dass man den Index als einen Führer für Tuberkulinimpfungen nicht mit Sicherheit benützen kann.

THE OPSONIC INDEX IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS.

By George P. Sanborn, M.D.,

New York.

The observations of Freeman, in October, 1906, cited by Wright,* that subsequent to massage of a gonococcal joint there ensued a fall in the gonoöpsonic power of the blood, and succeeding this fall a rise in the opsonic power,—a sequence of negative and positive phases, similar in all respects to the variation in opsonic power which Wright has shown follows the injection of a gonococcus or other vaccine in sufficient dosage,—led to the conclusion that in these phenomena he was dealing with an immunizing response to a vaccine consisting of living bacteria and their products, that had emanated from an infected focus, and was dispersed into the lymph and blood-stream by the massage.

Starting from this observation, a series of investigations† were carried out by Wright and his assistants in order to determine the effect on the opsonic power of the blood of massage, passive and active exercise, passive congestion, hot fomentations, operative procedures in localized infectious processes, and so forth; and in pulmonary tuberculosis the effect of measures and manipulations that were calculated actively to stir up the focus of infection, such as deep breathing, percussion of the chest, and exercise. All these measures were followed by variations in the opsonic index, which, in their correspondence to the sequence of opsonic events after inoculation with a sufficient dosage of vaccine, could be explained in no other way than as immunizing responses to auto-inoculations induced by these procedures. The investigations of Inman‡ as to the effect of exercise in the induction of variations in the opsonic index in a large number of cases of pulmonary tuberculosis furnish additional evidence that exercise is responsible for the phenomenon of auto-inoculation in this type of case.

The experience of Wright and others has shown that in individuals infected with the tubercle bacillus the tuberculo-opsonic power may be

* Lancet, August 24, 1907. † Lancet, November 2, 1907. ‡ Lancet, January 25, 1908.

continuously below normal; in other cases, generally above normal; in still others, fluctuating between subnormal and high. Further, in uninfected individuals the tuberculo-opsonic power shows, under all conditions of rest and exercise, but slight variation from a mean. If we look for a reason for the opsonic variations in infected cases, we must at once be impressed by the probability that they are governed by the varying degrees of auto-inoculation to which they are individually subject. The type* with which the subnormal opsonic power is associated obviously cannot be subject to auto-inoculation of any great degree, and it is to this class that strictly localized tubercle belongs, when, by reason of its location, it is free from any irritation or increase of blood-supply, due to the person's activity, and when, on account of its walled-off condition and its consequent defective blood-supply, it does not give up bacteria or their products to the circulation in sufficient amounts to constitute an auto-inoculation and to invoke an immunizing response. But, not only does the blood in these strictly localized cases fail to obtain sufficient stimulus from the focus to raise its opsonic power; it is also probable that its contact with the infected focus is reason for the loss of some of the opsonin that it is normally possessed of. Hence we find the low opsonic index in strictly localized tubercle.

The second type, in the fact of its usually high opsonic power, would presuppose repeated auto-inoculations in moderate amount; as an example I would cite cases of pulmonary tuberculosis that clinically give evidence of steady improvement.* The third type, with widely fluctuating tuberculo-opsonic index, would presuppose intermittent and severe auto-inoculation; example of this class in pulmonary tuberculosis in certain advanced cases and in incipient cases following activity. Further, there are certain cases of this disease at various stages whose opsonic power, under conditions of rest or moderate activity, shows very slight variation, but under the stress of a greater degree of activity shows decided fluctuations. In the one case there is obviously absence of auto-inoculation while at rest; in the other, the induced auto-inoculation of exercise.

It is my purpose to demonstrate some of the foregoing considerations regarding auto-inoculation and their application in diagnosis of pulmonary tuberculosis. With this in view I present a detailed study of the variations of the opsonic index in a case of pulmonary tuberculosis under conditions of rest, of ordinary activity, of hard work, under the stimulus of tuberculin b. e. inoculation, and finally under the influence of a supposed auto-inoculation, superimposed upon an inoculation of tuberculin b. e. The period of these observations extends over forty-five days, on thirty-seven of which one or more opsonic observations were made. This study was made in the laboratory and clinic of Professor Sir A. E. Wright, in October, 1907,

* A. E. Wright: Proceedings of the Royal Society, B, vol. lxxvii, 1906.

and I am indebted to him for this and many other opportunities enjoyed during my service in his laboratory.

In the determination of the opsonic indices Wright's method was, of course, closely adhered to—in fact, many of the blood specimens were examined as a part of the daily laboratory routine, though most of the work was done independently by the writer. The effect of the so-called "personal element" in the counting of the slides was eliminated in the first group by the fact that the slides were numbered and counted indiscriminately by any three or four observers; in the second group, constituting a majority of the observations, the slides were numbered by disinterested persons, so that the writer was at no time aware of the identity of the specimen he was counting.

The patient, a woman of thirty-five years, robust in appearance, had been treated in a sanatorium for some months. There was considerable cough and sputum, in which the tubercle bacilli were present. The temperature rarely reached 99° F., and she was able to be about her household duties continuously. There were definite signs in the left lung at the base.

The opsonic observations recorded in chart one were made for the purpose of answering the questions: Do auto-inoculations take place when under conditions of rest? Do auto-inoculations take place subsequent to hard work? The answer to the latter is to be found in the curve representing the variations subsequent to hard work October 24th. The two low indices registered on that day are succeeded by two high opsonic readings on the following day. To confirm this the same experiment was repeated November 4th, with an exactly similar result. You will note that indices were determined sufficiently often each day to rule out possible error to which any single opsonic index may be subject. To the first question, the record of November 2d and 3d indicates that no serious auto-inoculation occurred under resting conditions.

Passing to chart two, we find an answer to the question: Do auto-inoculations occur during periods of ordinary activity? It is evident that on three days, at least, no auto-inoculations are registered.

Further, to the proposition that if auto-inoculation be an actual equivalent in its nature to an inoculation of tuberculin, and vice versâ, there should be registered variations in the opsonic index that should correspond closely in their characteristics, we have here evidence to suggest an affirmative answer; for after an injection of tuberculin, $\frac{1}{20000}$ milligram, given October 8th, there was registered on the following day a rise in the index corresponding to those produced by induced auto-inoculation. A criticism of this curve is valid, since the one index recording the maximum might be due to error.

We have, however, in chart three, following inoculation of $\frac{1}{15000}$ milligram, a repetition of the effect shown in chart two. From a priori consid-

erations we should expect a more prolonged elevation of the opsonic power from this slightly larger dose, and a glance at chart three, from November 18th to November 23d, shows this to have been the case.

Experience has shown that a dose of tuberculin sufficient to produce an elevation of opsonic power without producing a negative phase previous to the rise may be increased to the extent of producing a negative phase of a day's duration without injury and with the chances of a much more prolonged positive phase succeeding. Therefore in the absence of a negative phase November 18th and 19th it was considered wise to increase the dosage at the next inoculation.

Chart four shows the effect of $\frac{1}{10000}$ milligram tuberculin. There is recorded a sharp rise on the following day, but there were subsequently a rapid sinking away and a prolonged period of subnormal opsonic power or negative phase. On December 3d or 4th I learned that the patient was ill, and I saw her at her home. She had a high temperature, rapid pulse and respiration, dusky color, diffuse râles. Admitted to the hospital, her temperature became normal after ten days or so, recovery being associated with an elevated opsonic index. As it scarcely seems possible that this dosage was too large, and in the light of her admission that she had overworked soon after her inoculation, it seems probable that in this slump in opsonic power and subsequent exacerbation we were dealing with a severe auto-inoculation superadded to the tuberculin given. This is a constant danger when tuberculin is given in ambulatory cases in which activity cannot be controlled. Further study of these charts might bring up many interesting points not having to do with diagnosis, but I will omit consideration of these.

The phenomenon of auto-inoculation, as registered by variations in the opsonic index, as described by Wright, investigated by Inman and others, and demonstrated in this study in its application to pulmonary tuberculosis, as met with in this disease, may then be either spontaneous or induced. In normal individuals, as has been already stated, tuberculo-opsonic index conforms closely to a mean under all conditions of rest and activity, and this absence of variation is consistent with the absence of tubercular focus. Variations in the infected cases presuppose an active tubercular process, from which the auto-inoculations emanate.

The meaning of a non-production of auto-inoculation in suspected cases may be either that exercise is insufficient or the disease process is already arrested, or that the patient has not pulmonary tuberculosis.

A simple method for diagnosis is that shown in the accompanying chart. Some sort of exercise on one day sufficient to increase the respiratory activity, an opsonic determination before exercise, again after exercise, and twice on the following day. A variation of more than twenty points would be

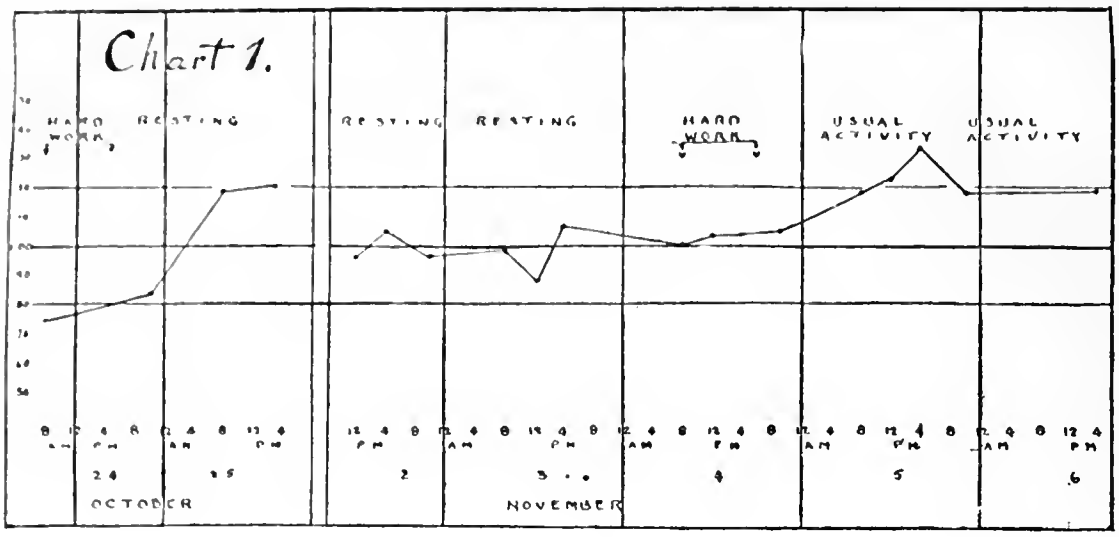


Chart 1.
HARD WORK
RESTING
RESTING
RESTING
HARD WORK
USUAL ACTIVITY
USUAL ACTIVITY
OCTOBER
NOVEMBER

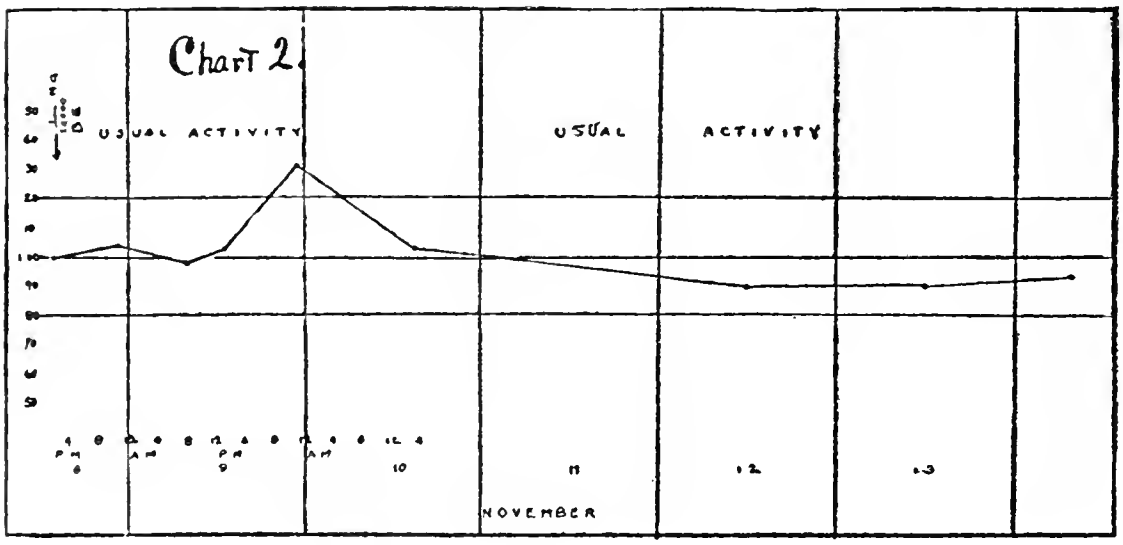


Chart 2.
USUAL ACTIVITY
USUAL
ACTIVITY
NOVEMBER

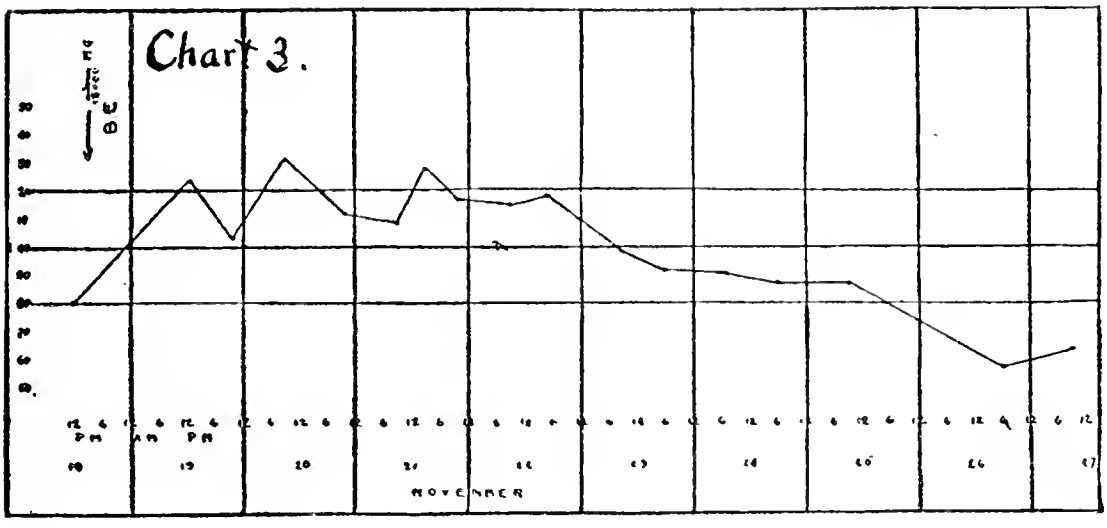


Chart 3.
NOVEMBER

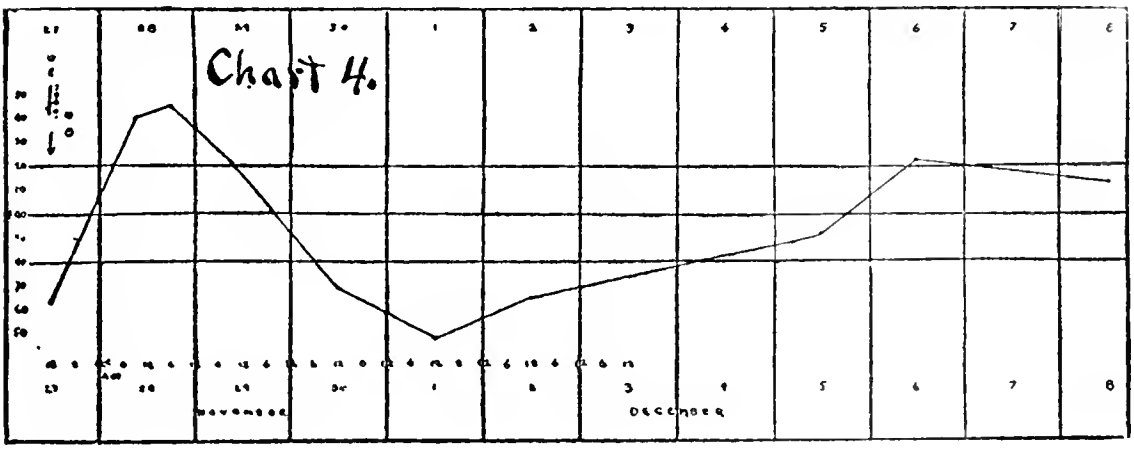


Chart 4.
DECEMBER

evidence of probable pulmonary tubercle, and if similar results were obtained after a second experiment, the evidence should be sufficient for a diagnosis. Variations of less than twenty points, if repeated, should not be entirely disregarded if the technic is up to the standard.

A second method is to make opsonic determinations from day to day, the patient going about as usual. Wide fluctuations may thus be registered, and a doubtful diagnosis may thus be made certain.*

The method that Inman has originated is quite as applicable to diagnosis as it is to the decision of questions of treatment. He exercises the patient immediately upon rising in the morning for half an hour or so, determines the opsonic index before the exercise, after exercise, and several times during the first five or six hours following. He finds that positive cases quite consistently yield variation; that arrested cases may show little or no variation; that sufficient exercise in cases of active processes may produce a rise or a fall in the tuberculo-opsonic power during the first few hours, depending on whether at the start the opsonic index was low or high. If the index is at first low, a rise takes place; if high, there is usually a drop. This early variation is met with after inoculation with vaccines, and is usually in the direction of a rise, designated by Wright a false rise, since this early rise is followed by the usual negative phase. It remained for Inman to describe a like variation in the first few hours after an induced auto-inoculation, and to make use of it for diagnosis successfully. Its advantage over other methods lies in the fact that all the blood specimens can be tested at one time, which is conducive to accuracy and saves time.

It should be necessary to make use of these methods only when the evidence obtained by the usual clinical methods is insufficient for diagnosis. I should not for a moment favor a less careful clinical study of a case, nor should I offer these methods to be used to the exclusion of such careful study, but I should be strongly inclined, in cases where diagnosis is uncertain, not to resort to the old tuberculin test, nor to the eye reaction of Calmette, nor to the sending of the patient to a tuberculosis sanatorium on chances, but to study the case somewhat in the manner suggested, and thus to avoid the discomfort of the eye reaction, the discomfort and possible danger of the old tuberculin test. The skin reaction of von Pirquet seems an excellent test, but the disadvantage is that it does not localize. On the other hand, ruling out local or forms of tuberculosis other than pulmonary, of a sort that might be stirred up by the exercise we prescribe, sufficiently to auto-inoculate any variations produced by the exercise, should be interpreted as evidence of the presence of a pulmonary lesion, given suspicious local signs.

The disadvantages of using the opsonic index for diagnosis would at present seem to lie in the difficulty of securing reliable opsonic indices,

* Wright: Lancet, November 2, 1907.

under the present methods; and this seems to be the result not of a lack of ability on the part of good laboratory men to carry out Wright's technic properly, but because it not only requires careful technical training, but patience, enthusiasm, and a considerable portion of one's time to carry out the laboratory details and to keep sufficiently in practice to turn out accurate work.

El Index Opsónico en el Diagnostic de la Tuberculosis Pulmonar.— (SANBORN.)

Un estudio detallado del indice opsónico-tuberculoso en los casos de tuberculosis pulmonar, bajo las condiciones del descanso, la actividad moderada, durante el trabajo fuerte y despues de la inyeccion de la tuberculina B. R., durante un periodo de cerca de dos meses en la historia del paciente, con una determinacion de de una á tres veces en el dia del indice opsónico durante la mayor parte del periodo, fue hecho en la clinica del Professor Sir A. E. Wright, en Noviembre de 1907, con una extricta observacion de su metodo. Los esfuerzos fueron de obtener los hechos que pudieran dar una base especifica al tratamiento; estudio del grado de auto-inoculacion del paciente de su propia actividad.

El estudio del experimento demuestra los resultados siguientes:

1. El descanso y el trabajo ligero pueden ser compatibles con el indice opsónico normal.

2. El trabajo fuerte, sinembargo, produce un aumento en el poder opsonico (auto-inoculacion.)

3. La correspondencia entre el efecto del ejercicio y el de la tuberculina, en el indice opsónico es evidente, lo cual sugiere la similaridad del estimulo. La aplicacion de este en el diagnostico, por lo tanto, depende de la variacion del indice opsónico despues del ejercicio. El ejercicio deberá ser variado segun el caso. Tres metodos de aplicacion. Las ventajas de tales metodos son:—

1. La ausencia de los efectos desagradables de la tuberculina y mas exacto que esta.

2. Se evita la conjuntivitis que produce el metodo de Calmette.

3. Mayor exactitud en la localizacion de la que es posible con ambas ó con la reaccion de von Pirquet.

Las desventajas.

THE ACCURACY OF THE TUBERCULO-OPSONIC INDEX, AND ITS VALUE AS A CONTROL TO TUBERCULIN TREATMENT IN PULMONARY TUBERCULOSIS.

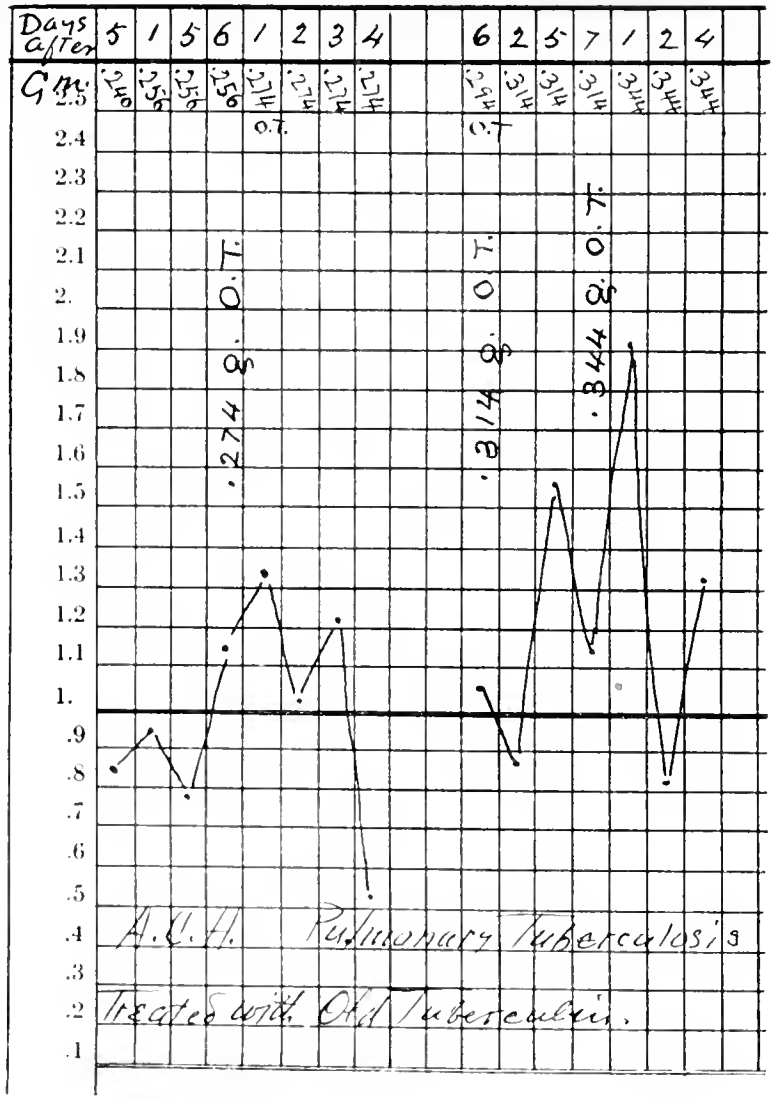
By Drs. Hugh M. Kinghorn, David C. Twichell, Norman M. Carter, and F. W. O. Werry, B.A.,

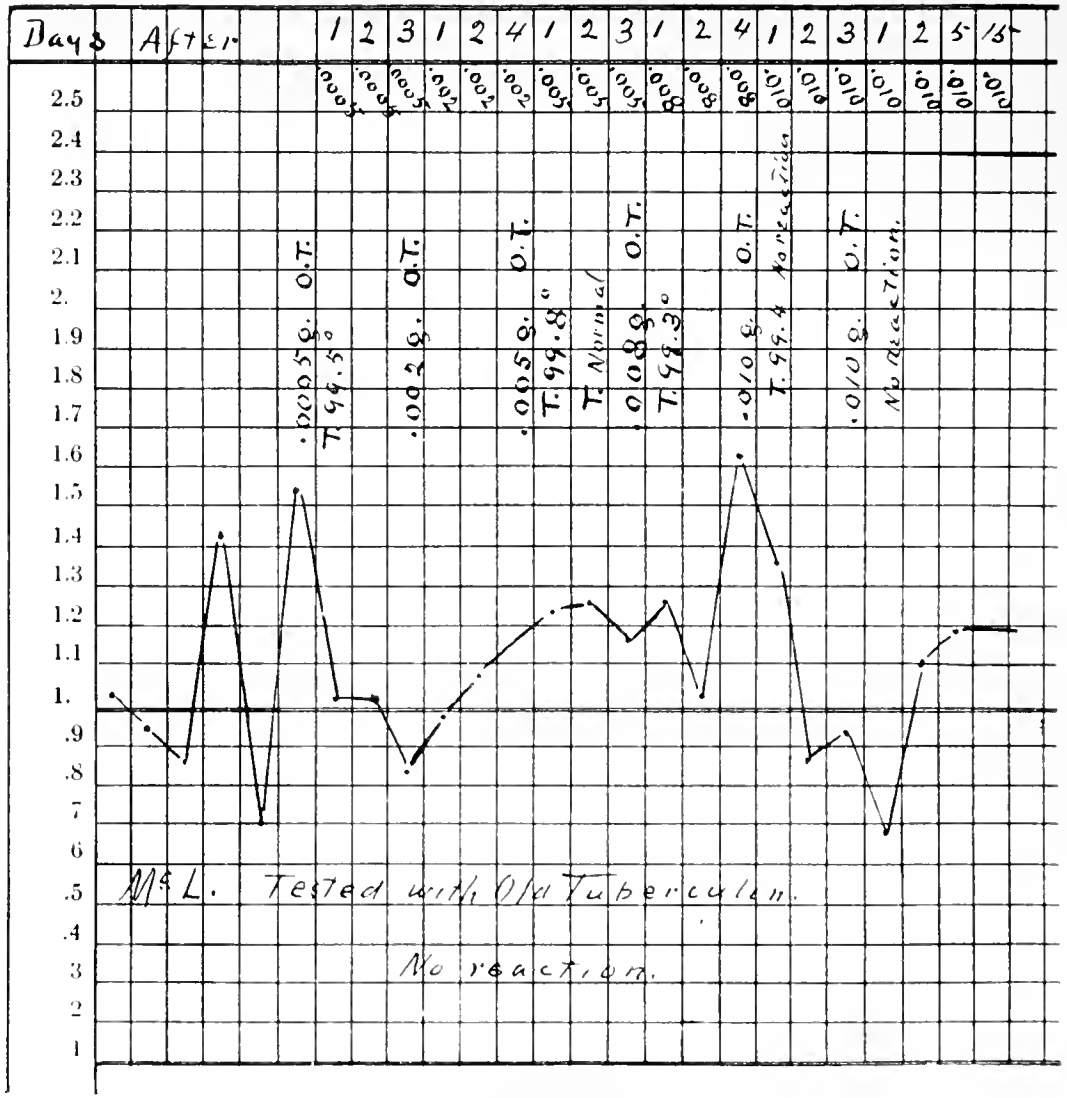
Saranac Laboratory for the Study of Tuberculosis, Saranac Lake, N. Y., Dr. E. L. Trudeau, Director.

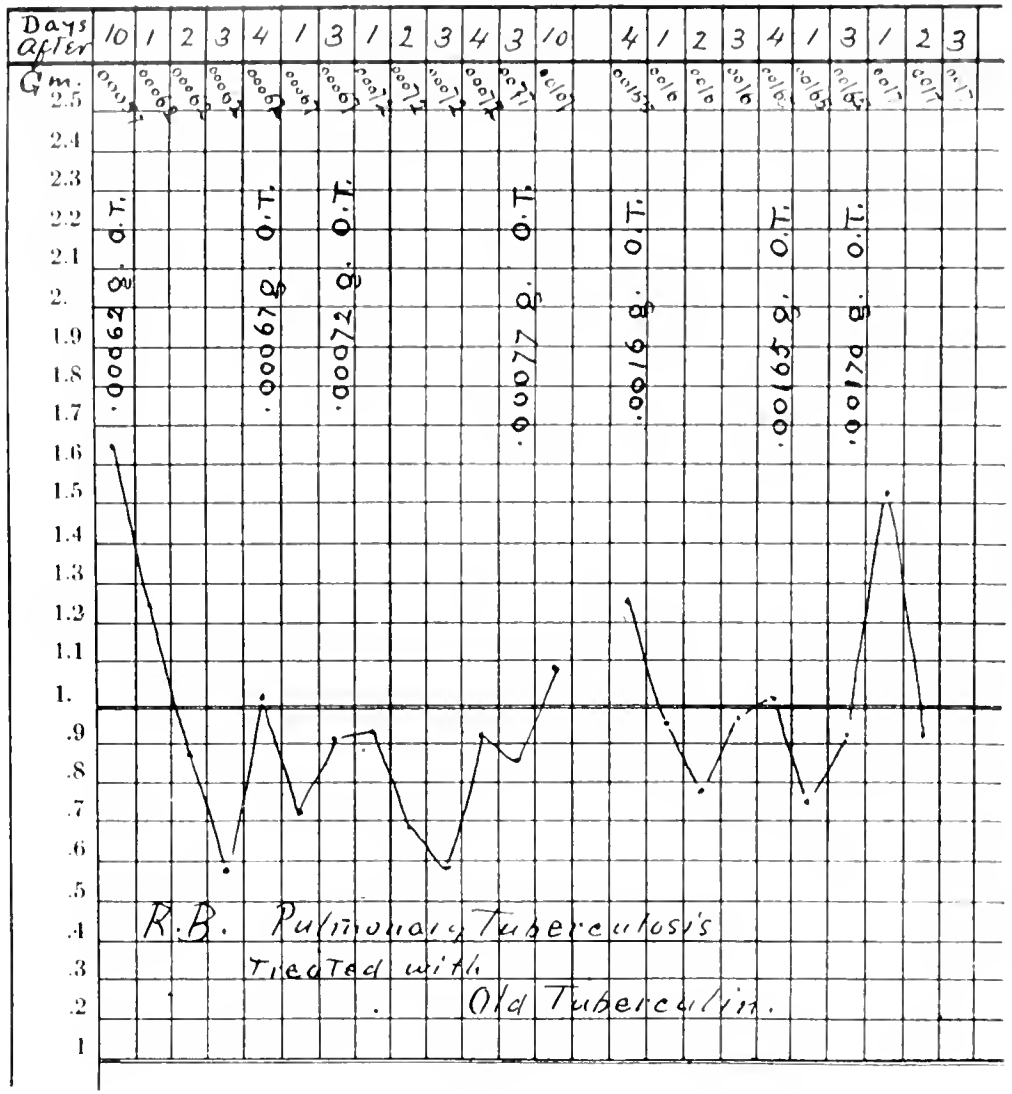
Since Professor Wright's first publications on vaccine therapy and the opsonic index, work has been done with the tuberculo-opsonic test at the Saranac Laboratory with a view to try and establish the fact as to whether the test can be put into practical use in the diagnosis and treatment of pulmonary tuberculosis. At this time we will deal with the accuracy of the test and its value as a control to tuberculin treatment. At some future date we hope to give our results as to the value of the test in diagnosis. For a considerable time it was necessary to devote ourselves to technic in order to obtain reliable results. The difficulties in the way of making accurate tests were not slight, but they were gradually overcome, so that we now feel our results are as accurate as those which have been published by most other workers.

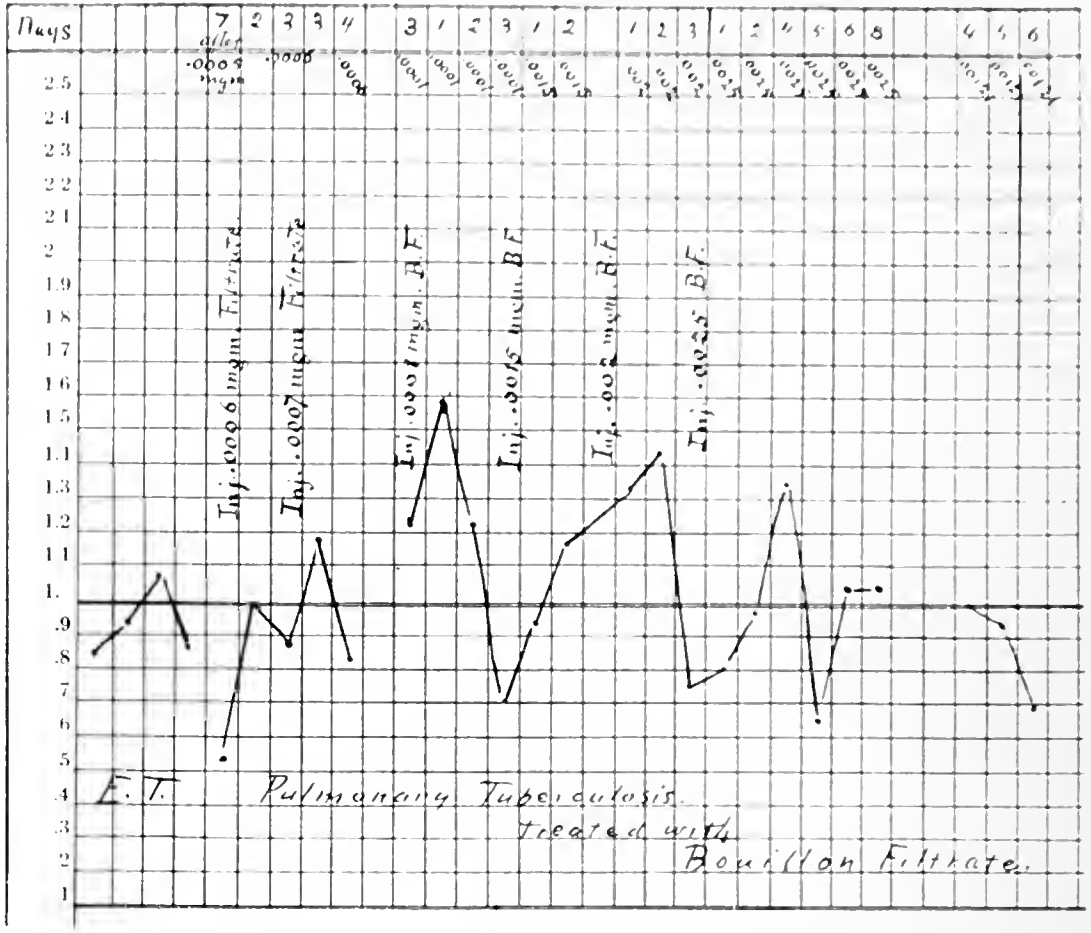
Technic.—Our technic is the same as that of Professor Wright, and has been described in the Transactions of the National Association for 1906 and 1907. The only modification is in preparing the emulsion. Our method is that of Dr. E. R. Baldwin, and was described in the article referred to above (1907).* It has proved wholly satisfactory. We try to have the strength

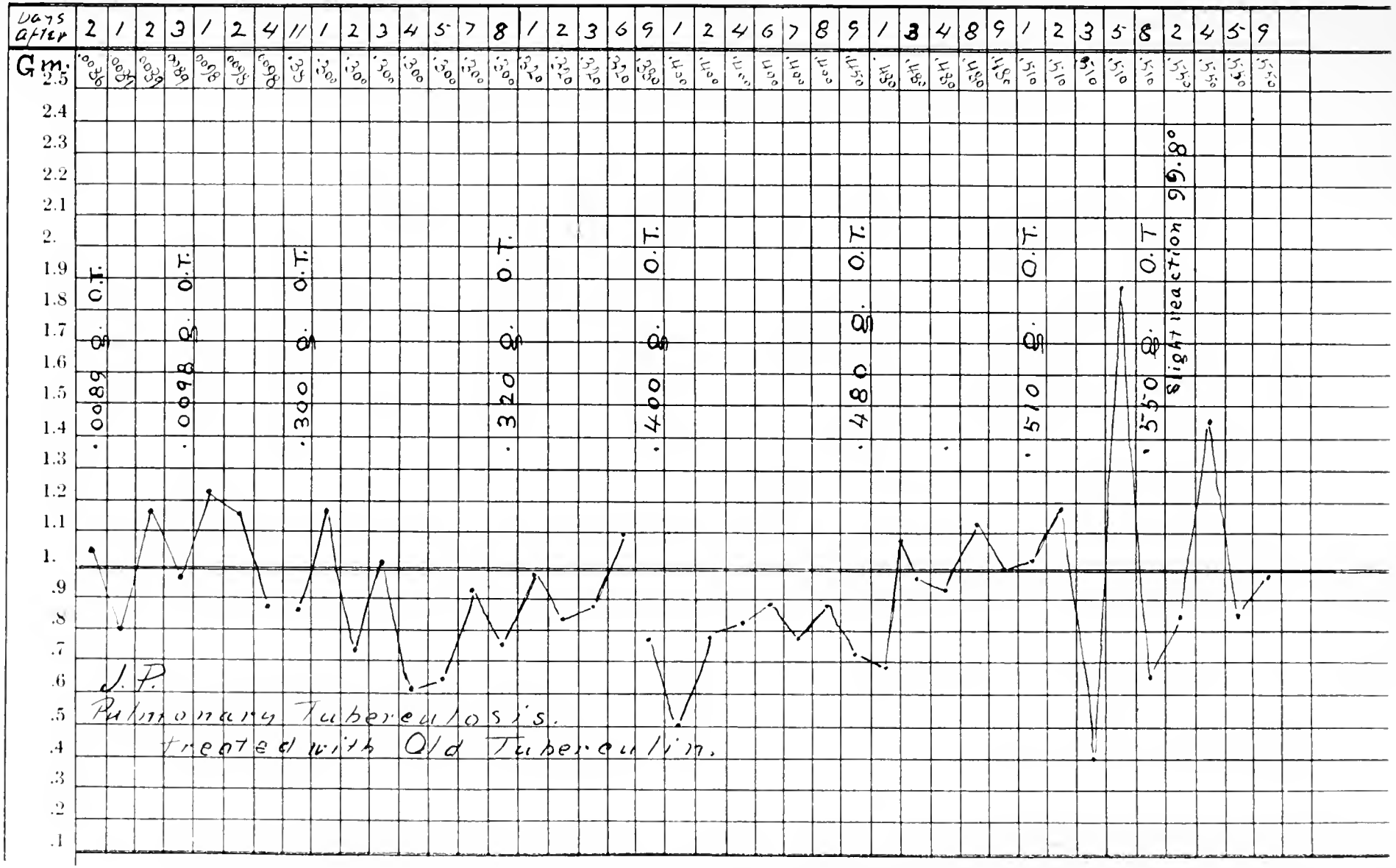
* A quantity of washed and dried tubercle bacilli from broth cultures was weighed and then moistened with distilled water, and sterilized in the autoclave at 110° C. for fifteen minutes. Enough water to make a muddy mass was then added, and they were rolled for six hours in a porcelain mill with porcelain balls to break up the clumps. They were then removed from the mill by washing it out with distilled water. The resulting emulsion, which contained 4 grams of bacilli in 115 c.c of water, was preserved by the addition of formalin in the proportion of 1 to 1250 (phagocytosis is not disturbed by this amount of formalin). It was then measured off into small tubes, which contained 0.1 c.c. each. In utilizing this emulsion the contents of a tube are thoroughly mixed with 2 c.c. of a sterile 1.5 per cent. NaCl solution, and centrifugalized fifteen minutes with a water centrifuge. We find that emulsions prepared from these

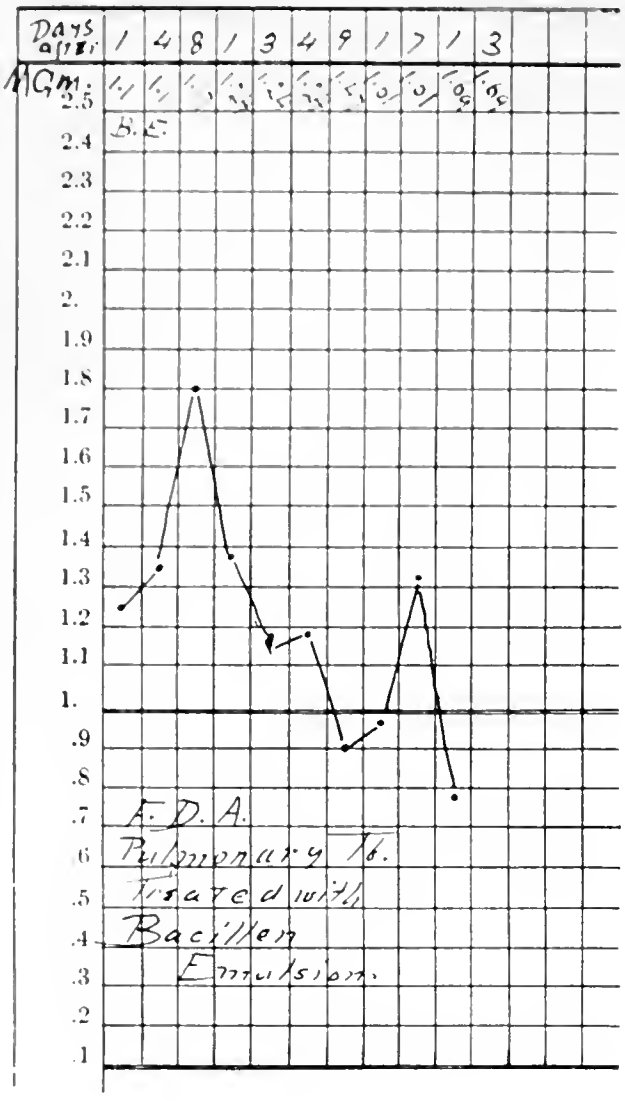

Days after
5 1 5 6 1 2 3 4 6 2 5 7 1 2 4
Gm.
.274 g. O.T.
.314 g. O.T.
.344 g. O.T.
A.C.H. Pulmonary Tuberculosis
Treated with Old Tuberculin.

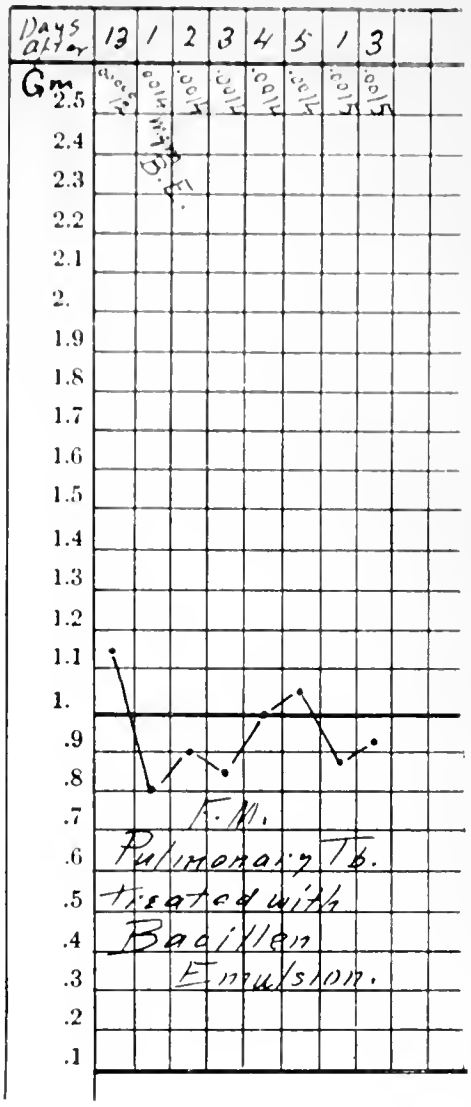

Days After
.0055 g. O.T. T. 99.5°
.0029 g. O.T.
.0055 g. O.T. T. 99.8° T. Normal
.0088 g. O.T. T. 99.2°
.010 g. O.T. T. 99.4 Morning
.010 g. O.T. No Reaction.
Mc L. Tested with Old Tuberculin.
No reaction.

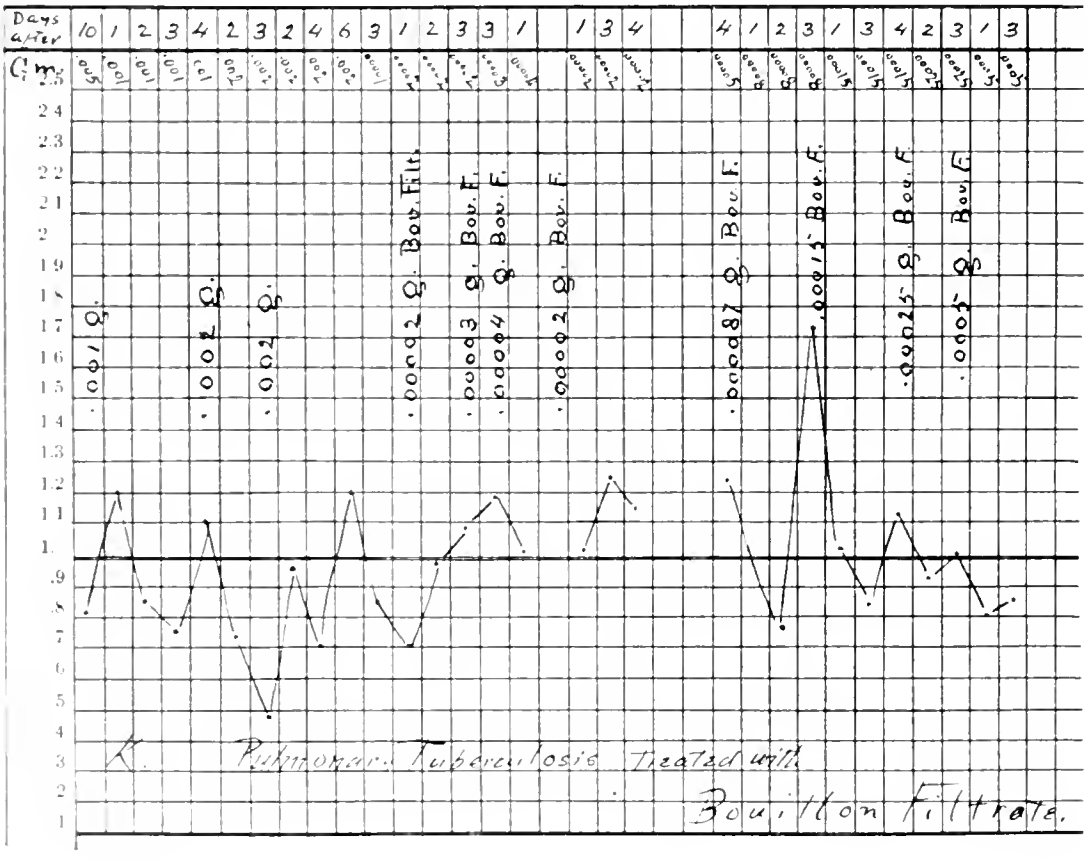

Days after
Gm.
.00062 g. O.T.
.00067 g. O.T.
.00072 g. O.T.
.00077 g. O.T.
.0016 g. O.T.
.00165 g. O.T.
.0017 g. O.T.
R.B. Pulmonary Tuberculosis
Treated with
Old Tuberculin.

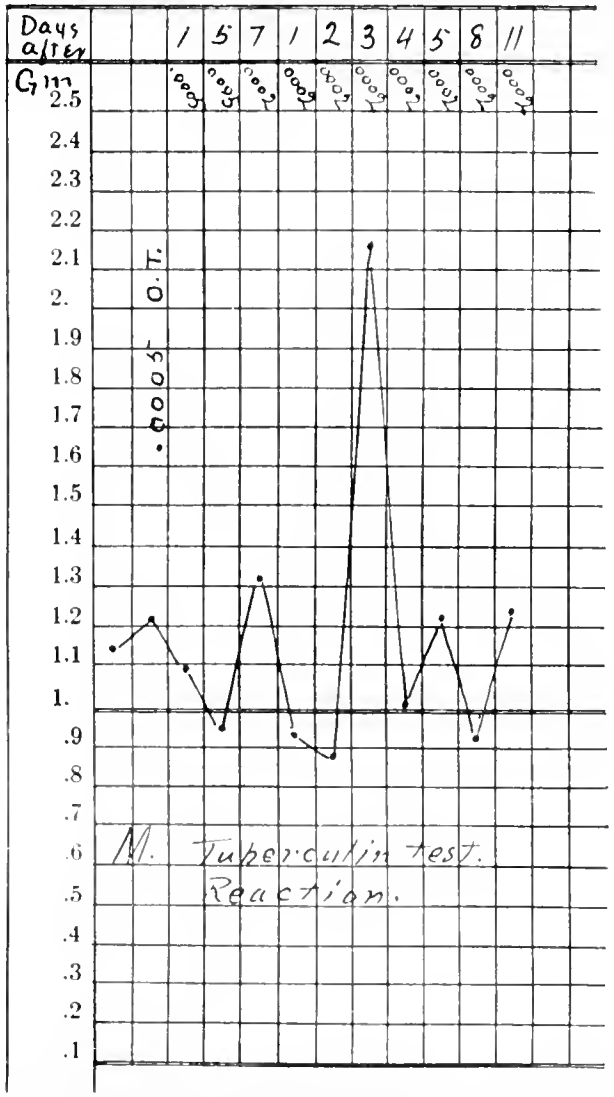

Days
Inj. .0006 mgm. Filtrate
Inj. .0007 mgm. Filtrate
Inj. .0001 mgm. B.F.
Inj. .0015 mgm. B.F.
Inj. .002 mgm. B.F.
Inj. .0025 B.F.
E.T. Pulmonary Tuberculosis
Treated with
Bouillon Filtrate.


Days After
Gm.
O.T.
.0089 Gm.
O.T.
.0098 Gm.
O.T.
.300 Gm.
O.T.
.320 Gm.
O.T.
.400 Gm.
O.T.
.480 Gm.
O.T.
.510 Gm.
O.T.
.550 Gm.
slight reaction 99.8°
J. P.
Pulmonary Tuberculosis.
treated with Old Tuberculin.

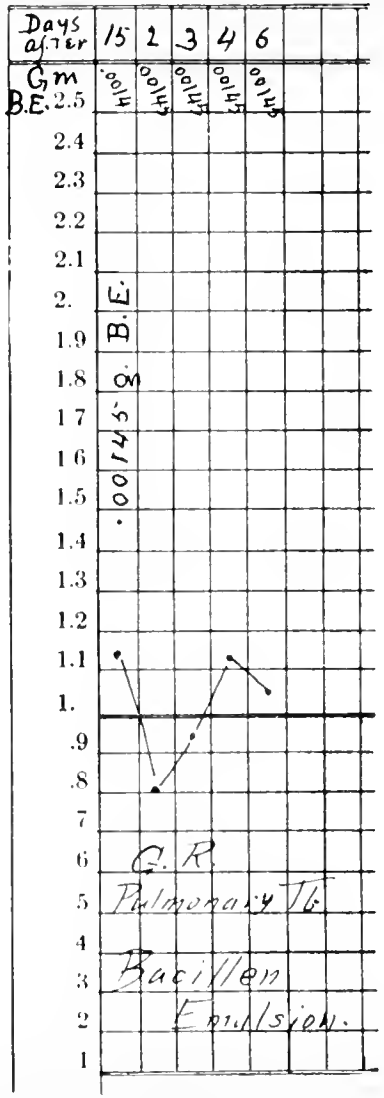

Days after
MGm.
B. E.
E. D. A.
Pulmonary Tb.
Treated with
Bacillem
Emulsion.

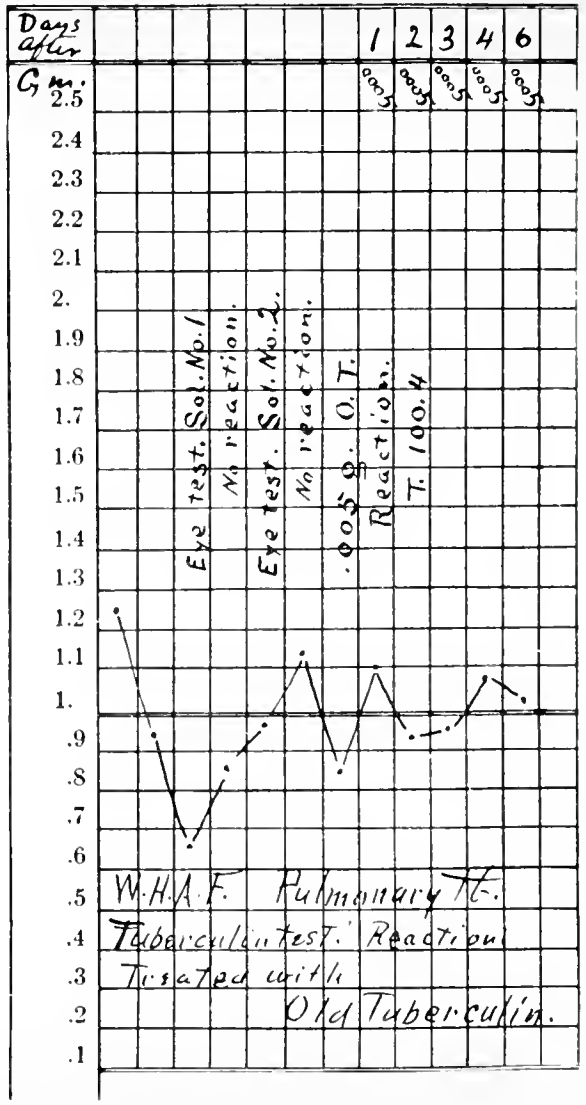

Days after
Gm.
E. M.
Pulmonary Tb.
Treated with
Bacillem
Emulsion.

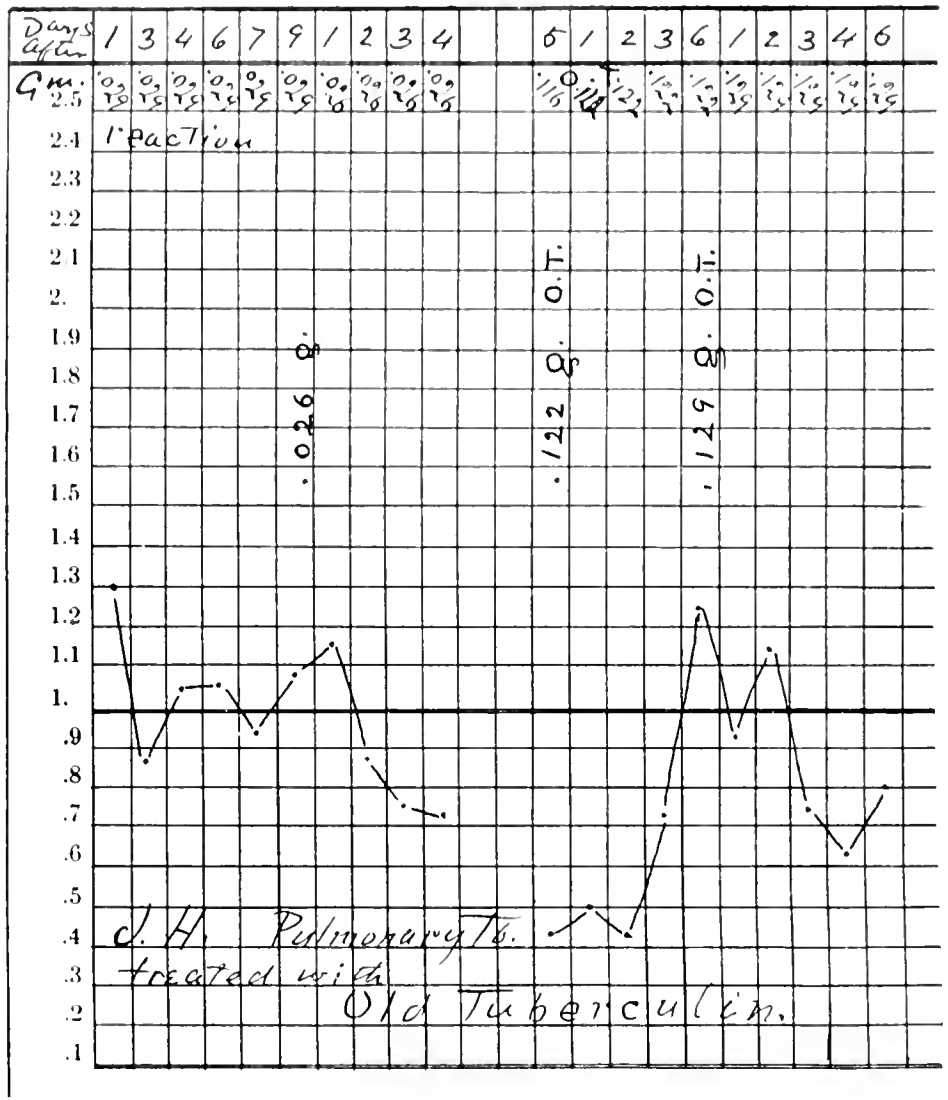

Days after
Gm.
.001 Q.
.002 Q.
.002 Q.
.0002 Q. Bov. Filt.
.0003 Q. Bov. F.
.0004 Q. Bov. F.
.0002 Q. Bov. F.
.00087 Q. Bov. F.
.0013 Bov. F.
.0025 Q. Bov. F.
.0005 Q. Bov. F.
K.
Pulmonary Tuberculosis Treated with
Bouillon Filtrate.

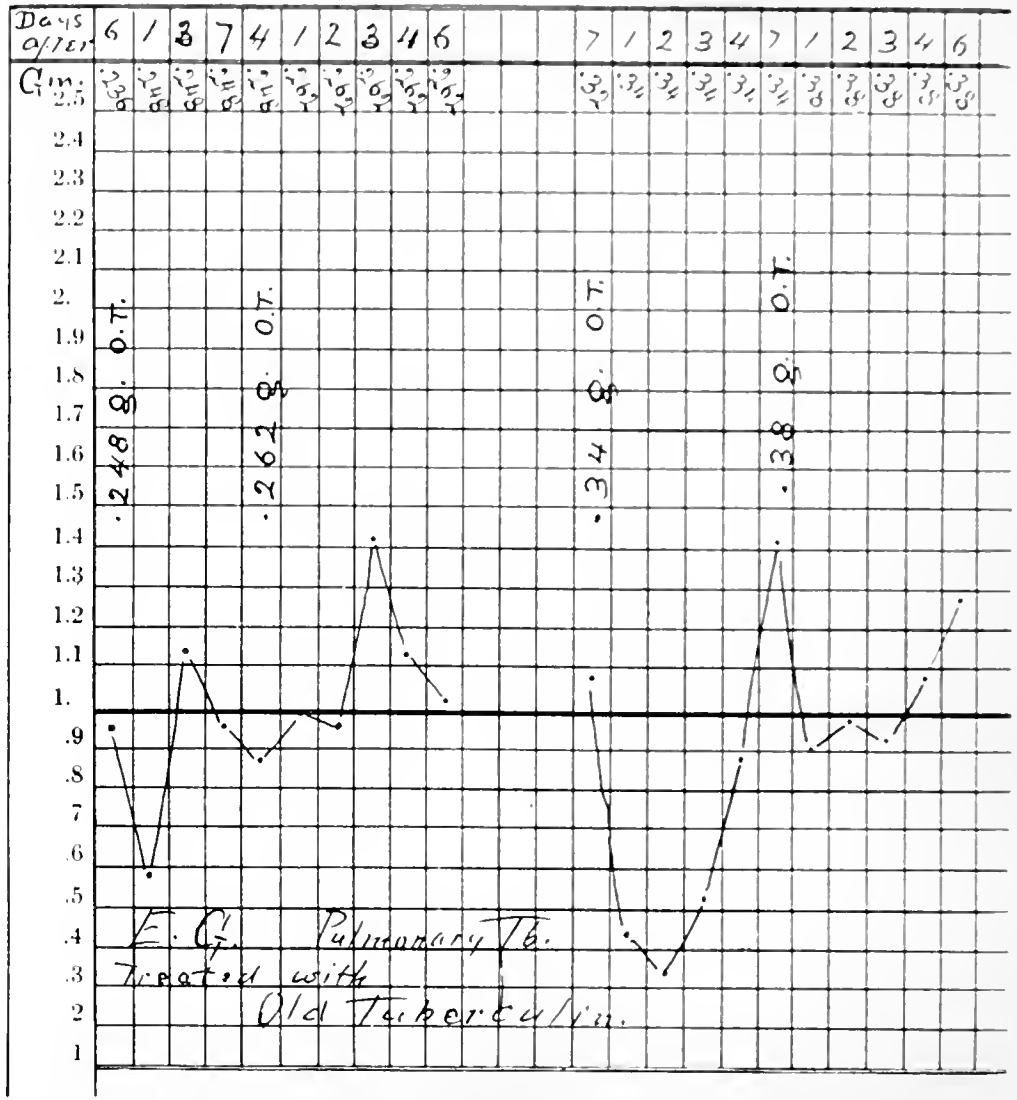


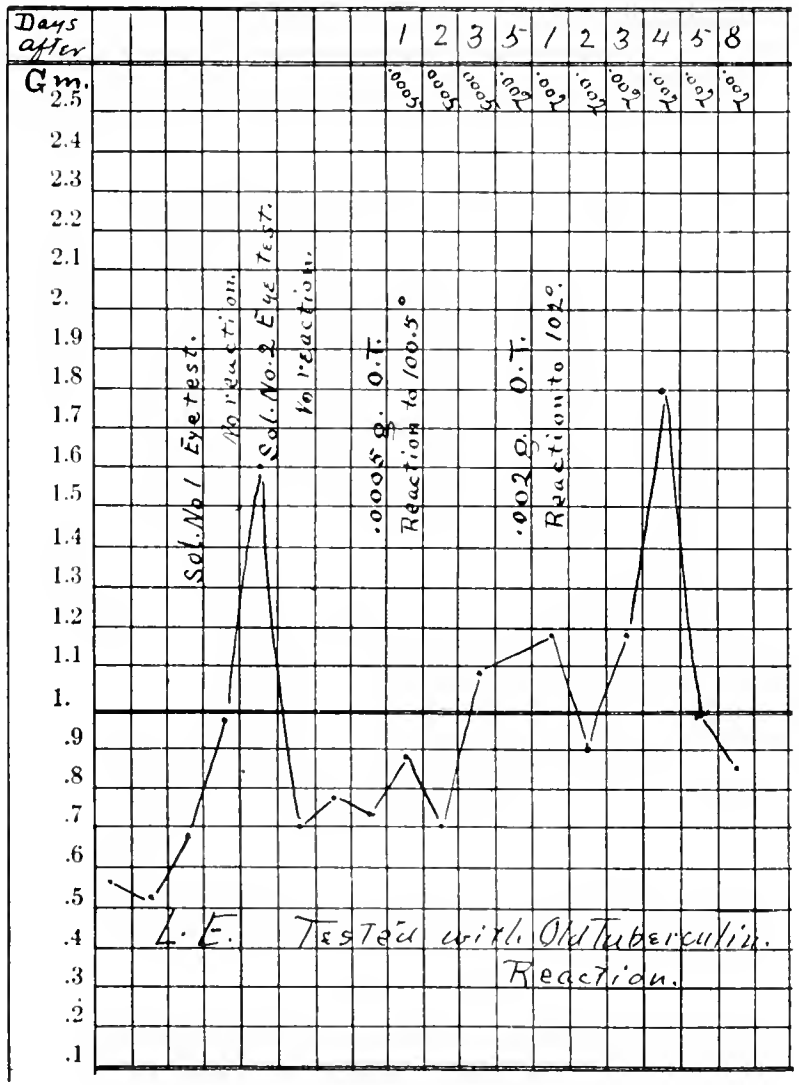
Bacillen Emulsion.

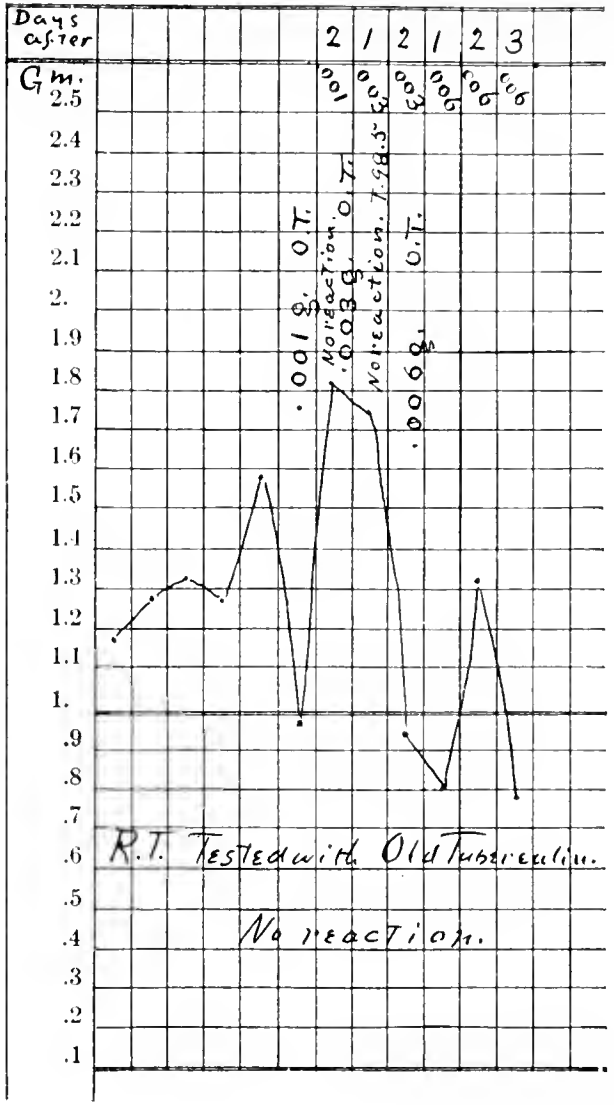


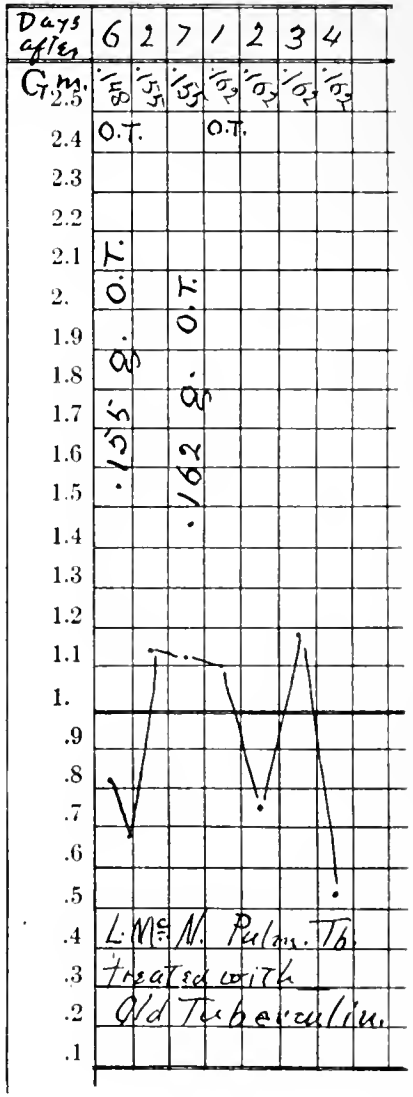



Days after
1 3 4 6 7 9 1 2 3 4 6 1 2 3 6 1 2 3 4 6
Gm.
2.5 2.4 2.3 2.2 2.1 2. 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1. .9 .8 .7 .6 .5 .4 .3 .2 .1
Reaction
.026 gr.
.122 gr. O.T.
.129 gr. O.T.
J. H. Pulmonary Tb.
treated with
Old Tuberculin.

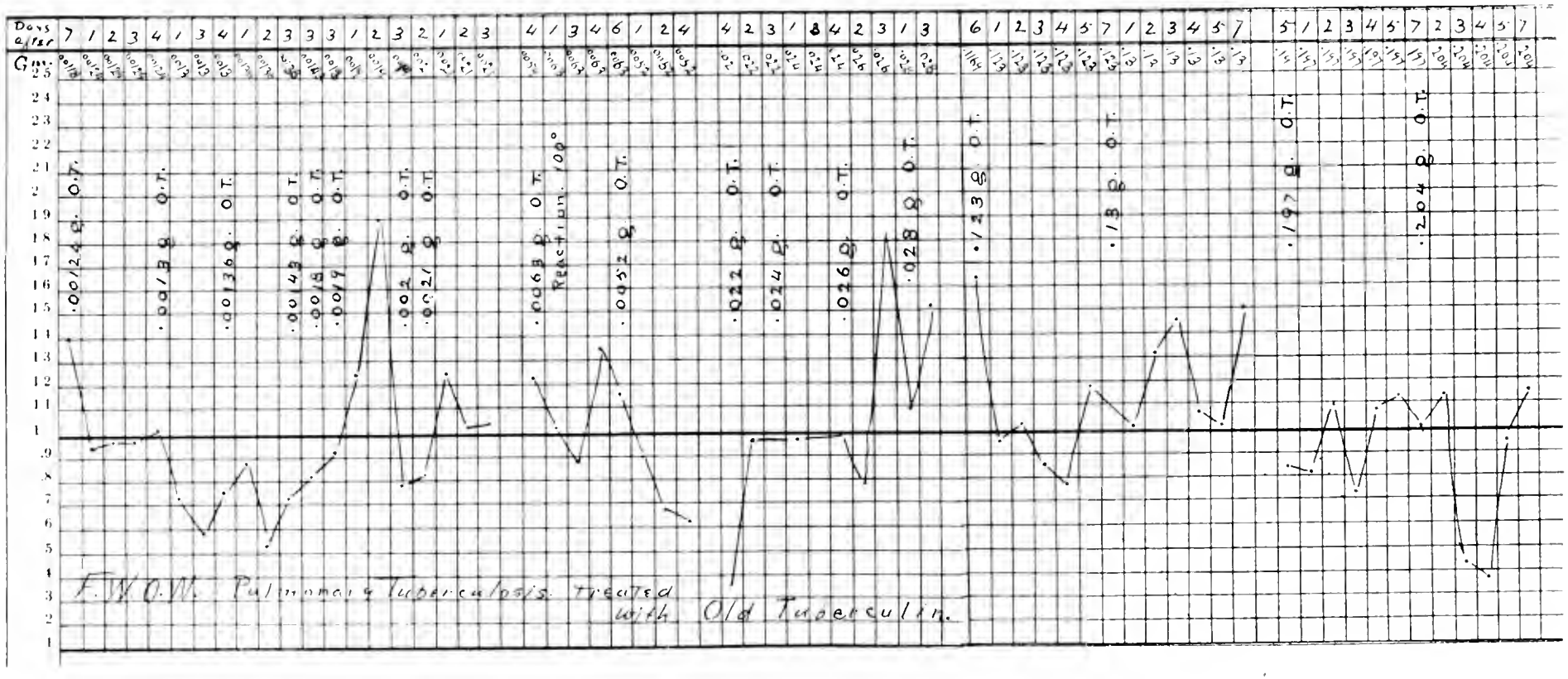

Days after
6 1 3 7 4 1 2 3 4 6 7 1 2 3 4 7 1 2 3 4 6
Gm.
2.5 2.4 2.3 2.2 2.1 2. 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1. .9 .8 .7 .6 .5 .4 .3 2 1
.248 gr. O.T.
.262 gr. O.T.
.34 gr. O.T.
.38 gr. O.T.
E. G. Pulmonary Tb.
Treated with
Old Tuberculin.

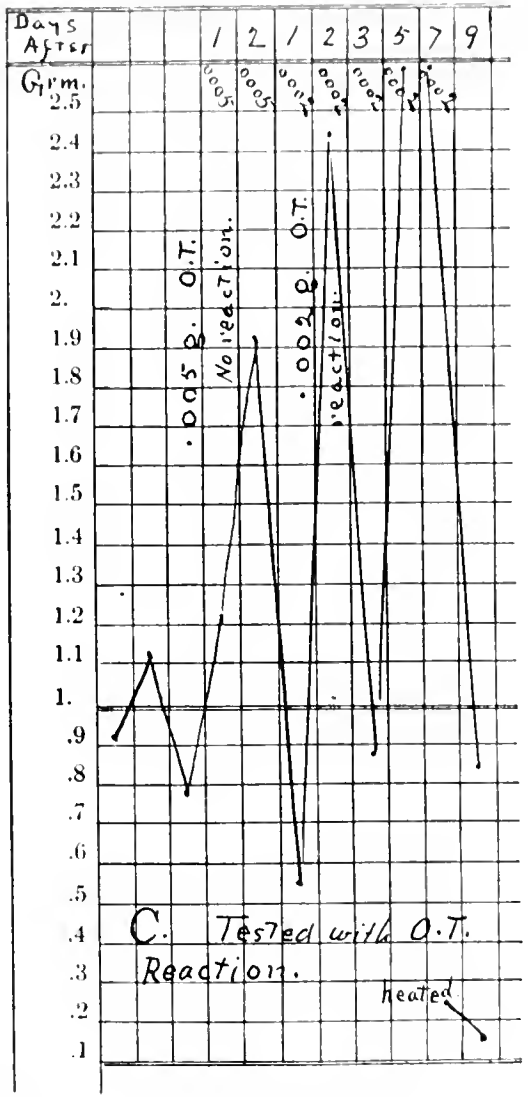

Days after
Gm.
1 2 3 5 1 2 3 4 5 8
.0005 .0005 .0005 .001 .002 .002 .002 .002 .002 .002
Sol. No 1 Eyetest.
No reaction.
Sol. No 2 Eye test.
No reaction.
.0005 g. O.T.
Reaction to 100.5°
.002 g. O.T.
Reaction to 102°
L. E. Tested with Old Tuberculin.
Reaction.

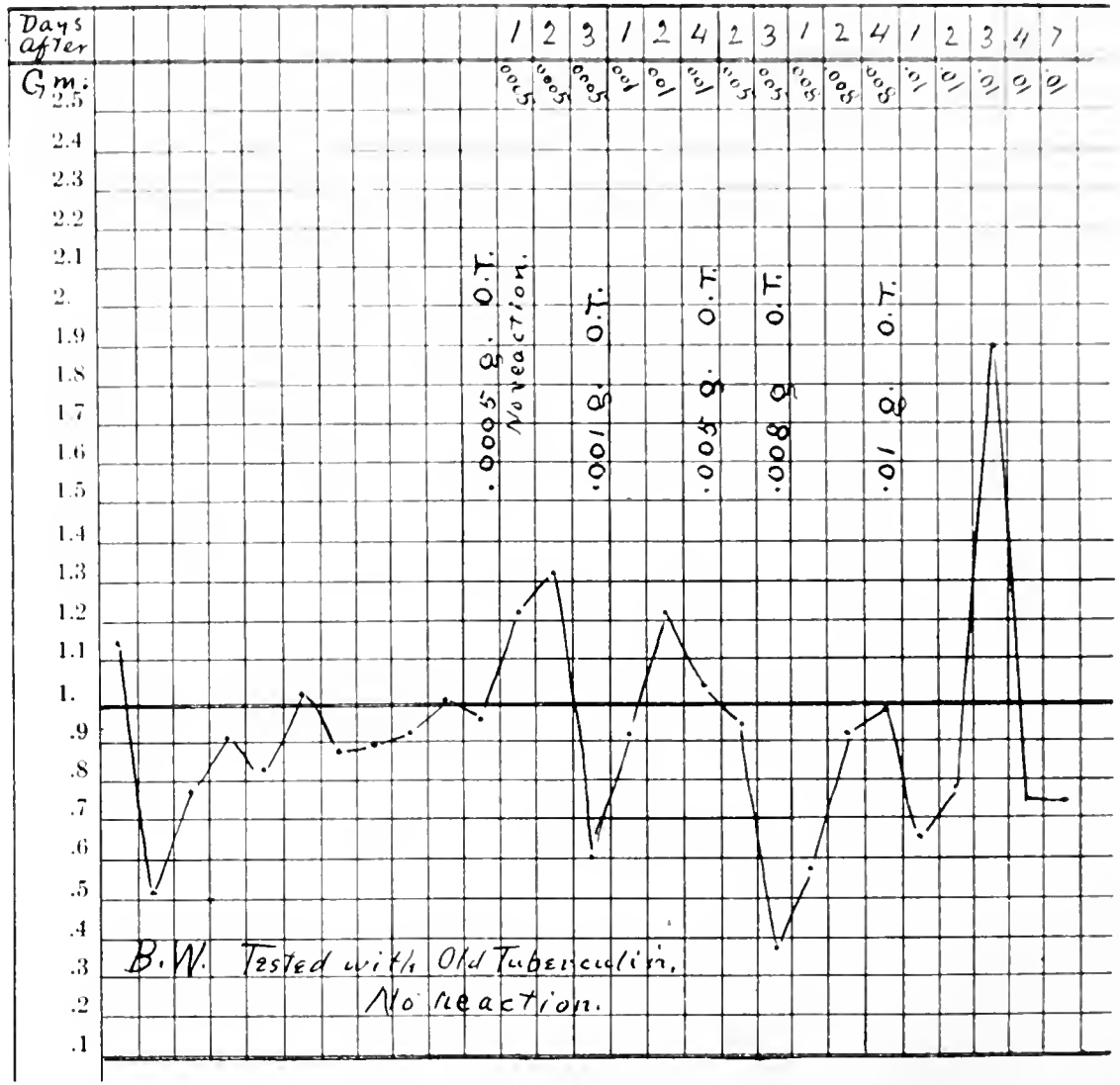

Days after
Gm.
2 1 2 1 2 3
.001 .003 .003 .006 .006 .006
.001 g. O.T.
No reaction. .003 g. O.T.
No reaction. T. 98.5°
.006 g. O.T.
R.T. Tested with Old Tuberculin.
No reaction.

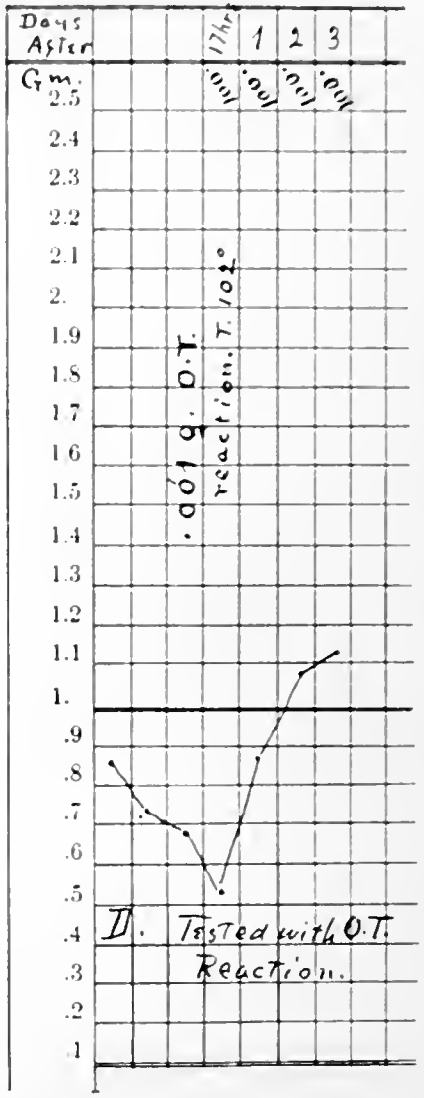

Days after
Gm.
6 2 7 1 2 3 4
.148 .155 .155 .162 .162 .162 .162
.135 g. O.T.
.162 g. O.T.
L. Mc. M. Pulm. Tb.
Treated with
Old Tuberculin.

Old Theatre
Theatre Audiences


Days after
Grs.
.00124 g. O.T.
.00139 g. O.T.
.00136 g. O.T.
.00148 g. O.T.
.00158 g. O.T.
.00179 g. O.T.
.002 g. O.T.
.00221 g. O.T.
.0068 g. O.T.
Reaction 100°
.0452 g. O.T.
.022 g. O.T.
.024 g. O.T.
.0260 g. O.T.
.028 g. O.T.
.1395 g. O.T.
.138 g. O.T.
.197 g. O.T.
.204 g. O.T.
F. W. O. W. Pulmonary Tuberculosis treated with Old Tuberculin.


Days After
1 2 1 2 3 5 7 9
Grm.
2.5 2.4 2.3 2.2 2.1 2. 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1. .9 .8 .7 .6 .5 .4 .3 .2 .1
.005 .005 .002 .002 .002 .002 .002
.005 g. O.T. No reaction.
.002 g. O.T. reaction.
heated
C. Tested with O.T. Reaction.


Days after
1 2 3 1 2 4 2 3 1 2 4 1 2 3 4 7
Grm.
2.5 2.4 2.3 2.2 2.1 2. 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1. .9 .8 .7 .6 .5 .4 .3 .2 .1
.0005 .0005 .0005 .001 .001 .001 .005 .005 .008 .008 .01 .01 .01 .01 .01
.0005 g. O.T. No reaction.
.001 g. O.T.
.005 g. O.T.
.008 g. O.T.
.01 g. O.T.
B.W. Tested with Old Tuberculin. No reaction.


Days After
17hr 1 2 3
Grm.
2.5 2.4 2.3 2.2 2.1 2. 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1. .9 .8 .7 .6 .5 .4 .3 .2 .1
.001 .001 .001 .001
.001 g. O.T. reaction. T. 102°
D. Tested with O.T. Reaction.

of the emulsion from 0.5 to 2 tubercle bacilli per cell. Beyond 2 bacilli per cell there is a liability to clumping, and counting is difficult. From 0.5 to 1 bacillus has proved the most satisfactory. In all our work only one control serum has been used (D.C.T.). Dr. Twichell is known to be absolutely free from tuberculosis, as he has never had subjective or objective symptoms of disease, and as he failed to react to 10 milligrams of Koch's old tuberculin. His serum was tested for four days against a pool consisting of equal parts of his own serum and of the serums of two men of the same physique as himself.

		Phagocytic Index.	Opsonic Index.
April 20, 1908,	Pool	0.85	1.00
	Dr. Twichell	0.81	0.95
	F. R.	0.75	0.88
	B. M.	0.81	0.95
April 22, 1908,	Pool	1.28	1.00
	Dr. Twichell	1.25	0.97
	F. R.	1.30	1.01
	B. M.	1.26	0.98
April 23, 1908,	Pool	0.92	1.00
	Dr. Twichell	0.93	1.01
	F. R.	0.88	0.95
	B. M.	0.97	1.05
April 24, 1908,	Pool	0.93	1.00
	Dr. Twichell	0.99	1.06
	F. R.	1.01	1.08
	B. M.	0.92	0.98

We shall see later on that the differences in the opsonic indices of these serums are within the range of error, which must be allowed in using the test. We also tested Dr. Twichell's serum against upward of 60 known healthy persons of both sexes, with the result that it stood 1.006 against the average of all. It is, therefore, reasonable to regard his as a standard serum. For this reason, and because it was not always convenient to obtain several healthy serums, and then make a pool, we used only Dr. Twichell's serum. We may also state that, throughout our whole work, his serum was obtained at the same or approximately the same hour as the test serum. This, however, is not necessary, as we have found his serum to change insignificantly during twenty-four hours, and, in fact, during a week's time.

small tubes are very uniform. A trial test should be made when the tubes are first used. When we know the amount of dilution which is required to have one or two tubercle bacilli per cell, the trial test is not necessary. An emulsion may frequently be used for a week. For instance, with the capsules we are at present using our daily routine is to draw off one part from the supernatant fluid near the top, and mix with two parts of 1.5 per cent. sodium chlorid solution, in order to have one tubercle bacillus per cell. The longer this supernatant fluid is used, the weaker it becomes, so that each day it needs to be diluted less.

D. C. T.'S SERUM AT DIFFERENT HOURS DURING THE DAY.

	Phagocytic Index.	Opsonic Index.
April 1, 1908, Pool of serums taken at 8, 10, 12, 2, 4, 6, 8, 10	0.70	1.00
Serum taken at 8 A. M.	0.77	1.10
" " " 10 A. M.	0.79	1.12
" " " 12 noon	0.75	1.07
" " " 2 P. M.	0.82	1.17
" " " 4 P. M.	0.69	0.98
" " " 6 P. M.	0.76	1.08
" " " 8 P. M.	0.73	1.04
" " " 10 P. M.	0.68	0.97
April 2, 1908, Pool of serums taken at 8, 10, 12, 2, 4, 6, 8, 10	1.12	1.00
Serum taken at 8 A. M.	1.07	0.95
" " " 10 A. M.	0.85	0.75
" " " 12 noon	1.15	1.02
" " " 2 P. M.	1.09	0.97
" " " 4 P. M.	1.24	1.10
" " " 6 P. M.	1.49	1.33
" " " 8 P. M.	1.18	1.05
" " " 10 P. M.	1.11	0.99
April 3, 1908, Pool of serums as above	0.64	1.00
Serum taken at 8 A. M.	0.58	0.90
" " " 10 A. M.	0.57	0.89
" " " 12 noon	0.62	0.96
" " " 2 P. M.	0.73	1.14
" " " 4 P. M.	0.72	1.12
" " " 8 P. M.	0.74	1.15
" " " 10 P. M.	0.66	1.03
April 4, 1908, Pool of serums	1.18	1.00
Serum taken at 8 A. M.	1.32	1.11
" " " 10 A. M.	1.23	1.04
" " " 12 noon	1.26	1.06
" " " 2 P. M.	1.26	1.06
" " " 4 P. M.	1.34	1.14
" " " 6 P. M.	1.47	1.25
" " " 8 P. M.	1.46	1.23
" " " 10 P. M.	1.30	1.10

In examining these four series of tests it might seem as though a normal serum varied at different hours during the day. Of 35 separate tests composing the four series, there are 6 tests which are outside the known mean error of our work, *i. e.*, beyond $\pm$ 14. One might contend that we worked with a control, which was not a "constant," and that we, therefore, estimated the value of a patient's opsonic power against a control, which might show very appreciable variations. Later on, however, we shall see just as great variations occurred when a considerable number of tests of the same serum were made. There is slight uniformity as regards the opsonic indices toward evening, but the tests are too few to say normal opsonins rise toward night. No conclusions can be drawn from these tests with regard to the influence of the ingestion of food on the opsonic index, as no regular change in the index can be observed following a meal. We have almost regularly observed, when from six to eight tests of the same serum are made, that one

or several of the tests will be extreme. We, therefore, think the extreme variations in the above series may just as likely be due to errors in technic as to variations in the amount of opsonin in the different specimens of serum. From this series of tests it would seem as if Dr. Twichell's serum, so far as the tubercle bacillus is concerned, shows little or no variation throughout the day and is a constant control. Fleming has also investigated the constancy of healthy serum and has reached the same conclusion. He found, with the tubercle bacillus, that the resistance of a healthy person is a very constant quality, and that the variation is little more than can be accounted for by the experimental error.

We also considered it of importance to determine how long a time opsonins remain unchanged in a serum; in other words, whether an interval of one or several days, or even a week, would influence the value of an opsonic test on a serum.

D. C. T.'S SERUM TESTED ON DIFFERENT DAYS.

December 20, 1907: December 20th, serum obtained at 10 A. M., considered as standard serum.

	Phagocytic Index.	Opsonic Index.
	0.51	1.00
December 20, 7.30 A. M., *i. e.*, 2½ hours old	0.59	1.16
" 19, 10.00 P. M., *i. e.*, 12 " "	0.45	0.88
" 19, 12.00 noon, *i. e.*, 22 " "	0.48	0.94
" 18, 10.00 A. M., *i. e.*, 2 days "	0.51	1.00
" 17, 10.00 A. M., *i. e.*, 3 " "	0.54	1.06
" 16, 10.00 A. M., *i. e.*, 4 " "	0.52	1.02
" 15, 10.00 A. M., *i. e.*, 5 " "	0.47	0.96
" 13, 10.00 A. M., *i. e.*, 7 " "	0.56	1.10

January 13, 1908: January 13th, serum obtained at 7.45 A. M., and considered as standard serum.

	Phagocytic Index.	Opsonic Index.
January 13, 7.45 A. M.,	0.87	1.00
" 12, 10.00 P. M., *i. e.*, 10 hours old	0.92	1.06
" 12, 10.00 A. M., *i. e.*, 22 " "	0.77	0.88
" 11, 10.00 A. M., *i. e.*, 2 days "	0.92	1.06
" 10, 10.00 A. M., *i. e.*, 3 " "	0.89	1.02
" 9, 10.00 A. M., *i. e.*, 4 " "	0.95	1.09
" 8, 10.00 A. M., *i. e.*, 5 " "	0.95	1.09
" 6, 10.00 A. M., *i. e.*, 7 " "	1.07	1.23

January 20, 1908: January 20th, serum obtained at 10 A. M., and considered as standard serum.

	Phagocytic Index.	Opsonic Index.
	1.21	1.00
January 20, 7.45 A. M., *i. e.*, 2½ hours old	0.96	0.79
" 19, 10.00 P. M., *i. e.*, 12 " "	1.07	0.88
" 19, 10.00 A. M., *i. e.*, 24 " "	1.27	1.05
" 18, 10.00 A. M., *i. e.*, 2 days "	1.30	1.07
" 17, 10.00 A. M., *i. e.*, 3 " "	1.20	0.99
" 16, 10.00 A. M., *i. e.*, 4 " "	1.04	0.86
" 15, 10.00 A. M., *i. e.*, 5 " "	1.18	0.98
" 13, 10.00 A. M., *i. e.*, 7 " "	1.24	1.02

January 27, 1908: January 27th, serum obtained at 10.30 A. M. and 7 A. M., and considered as standard serum.

	Phagocytic Index.	Opsonic Index.
		1.00
January 26, 10 P. M., *i. e.*, 12 hours old	1.05	1.01
" 26, 10 A. M., *i. e.*, 1 day "	1.00	0.96
" 25, 10 A. M., *i. e.*, 2 days "	1.22	1.16
" 24, 10 A. M., *i. e.*, 3 " "	1.18	1.13
" 23, 10 A. M., *i. e.*, 4 " "	0.99	0.95
" 22, 10 A. M., *i. e.*, 5 " "	1.01	0.97
" 20, 10 A. M., *i. e.*, 7 " "	1.13	1.11

From these tests it is thus seen the opsonin for tubercle of this normal serum did not diminish in the course of a week, and that it is quite safe to use this serum seven days old. It is also seen that one or several extreme variations from the normal are apt to occur, and, for the reasons above, we think these variations may just as likely be considered as due to errors in technic as to differences in opsonic content of the serums. Fleming also investigated this point and obtained similar results. He found the index of a normal serum to remain at normal for about a week, then to steadily fall until, at the end of a fortnight, it was reduced to about 0.50 or 0.60. With regard to the serum of infected persons he found the serums of different persons to vary very much in their keeping powers, and this without any relation to the index at the time the blood was drawn. From his figures the results obtained two or three days after the blood is drawn are quite trustworthy for pathological serums. Beyond this time, however, it is unsafe to rely on the tests.

In working with unheated serum we used only one washing to obtain the washed leukocytes, but were careful to wash with 15 c.c. of the citrated salt solution. For work with heated serum one washing is not sufficient, and we have always used three, though two washings are probably all that are needed. In passing we might say only the corpuscles of one of us (H. M. K.) were used in all the tests. We did this in order to avoid isoagglutination, as described by Hektoen.

EXPERIMENTS TO SHOW THE INFLUENCE OF WASHING CORPUSCLES ONCE OR SEVERAL TIMES.

		Phagocytic Index.
April 28, 1908:	D. C. T., unheated normal serum, corpuscles washed once	0.42
	D. C. T., " " " " " twice	0.46
	D. C. T., heated at 60° for ten minutes " " once	0.16
	D. C. T., " " " " " " " twice	0.08
	E. T., unheated tuberculous serum, " " once	0.42
	E. T., " " " " " twice	0.48
	E. T., heated " " " " once	0.37
	E. T., " " " " " twice	0.20

EXPERIMENTS TO SHOW THE INFLUENCE OF WASHING CORPUSCLES ONCE OR SEVERAL TIMES.—(*Continued.*)

			PHAGOCYTIC INDEX
April 29, 1908:	D. C. T., unheated normal serum, corpuscles washed	once	1.04
	D. C. T., " " " " "	twice	1.05
	D. C. T., heated " " " "	once	0.74
	D. C. T., " " " " "	twice	0.24
	E. T., unheated tuberculous serum " "	once	0.98
	E. T., " " " " "	twice	0.77
	E. T., heated " " " "	once	0.86
	E. T., " " " " "	twice	0.21
April 30, 1908:	D. C. T., unheated normal serum, corpuscles washed	once	0.95
	D. C. T., " " " " "	twice	1.55
	D. C. T., heated " " " "	once	0.57
	D. C. T., " " " " "	twice	0.15
	E. T., unheated tuberculous serum " "	once	0.66
	E. T., " " " " "	twice	1.09
	E. T., heated " " " "	once	0.58
	E. T., " " " " "	twice	0.15
July 2, 1908:	D. C. T., unheated normal serum, corpuscles washed	3 times	0.96
	D. C. T., heated " " " "	twice	0.05
	D. C. T., " " " " "	3 times	0.12
July 3, 1908:	D. C. T., unheated " " " "	3 times	0.52
	D. C. T., heated " " " "	twice	0.17
	D. C. T., " " " " "	3 times	0.19
July 4, 1908:	D. C. T., unheated " " " "	3 times	0.64
	D. C. T., heated " " " "	twice	0.06
	D. C. T., " " " " "	3 times	0.09

From these experiments it is seen one washing of leukocytes is not sufficient, inasmuch as there is apt to remain with the leukocytes enough opsonin to influence phagocytosis to a considerable degree. Our attention was directed to this fact while we were investigating heated tuberculous serums and serums obtained from persons with other acute diseases. We frequently found, when we washed the leukocytes only once, that the pathological heated serums had a high opsonic index, and that occasionally the opsonic index was higher with the heated than with the unheated serum. This occurred to a limited extent also with heated serums from healthy persons. The variations in the phagocytic indices in the above tests when the corpuscles were washed twice and three times were probably due to exposing the serum to different numbers of leukocytes. This fact has also been observed by other workers. Fleming found in all except one of his tests on this point that there was a higher reading obtained when fewer corpuscles were used. This difference was more marked in the higher dilutions of the washed corpuscles. While two washings of leukocytes seem to be sufficient, we now use three in all tests, whether with unheated or heated serum.

In former publications we stated we considered it to be necessary to count at least 100 cells in order to obtain a reliable estimate of the average phagocytic power of the cells. We see no reason to change this view. Even from this number of cells one is very liable to obtain an inaccurate result. We

feel quite sure that the chances of inaccuracy are very much increased by counting less than 100 cells. Our experience in counting duplicate slides has not been unfavorable. We have repeatedly found the variation between 100 cells from one slide and 100 cells from a duplicate slide to be not greater than that which exists when two series of 100 cells are counted on the same slide. The observer should count cells on that part of the slide which is suitably stained.

Accuracy of the Tuberculo-opsonic Test.

In order to obtain an estimate of the degree of accuracy of our work we made control tests at variable intervals. From three to six simultaneous tests of a healthy serum were made. Occasionally four simultaneous tests of one healthy serum were made for other purposes than to test accuracy. These tests were sometimes made by another worker, Dr. J. Woods Price. We have included them with the tests made solely as accuracy tests. We have, therefore, drawn our conclusions from the work done by three separate workers, and from largely the whole period of our work. The accuracy of all three workers is about the same. In this way we think we have reached a fair and unbiased conclusion of the value of the test as it is performed in the Saranac Laboratory. In all there were 100 control tests of the same serum divided into 23 separate series. This gives an average of 4.35 tests of the same serum to each separate series.

To estimate the accuracy of the test our object is to know the value of a single individual test against Dr. Twichell's serum. Given a test serum and Dr. Twichell's serum, how much margin on either side of the result are we to allow? We gain this result by finding the mean error of a single observation of the above-mentioned 100 tests of the same serum (Dr. Twichell's).

Mean Error of a Single Observation.

When several observations are made upon an unknown quantity, the best that can be expected is an approximation to the true value of that quantity.

In all observations of this nature errors will occur which may be classified under three headings: namely, instrumental; mistakes due to carelessness; unavoidable or accidental errors.

By careful adjustment of the instrument and great care in all particulars pertaining to the manipulation of the material instrumental errors may be largely eliminated.

All important work should be checked and real mistakes corrected.

Unavoidable errors are those which escape the notice of the most skilled workman, careful though he be in every detail of the observation.

The most expert marksman fails to hit the center of the bull's-eye at every shot. Let us consider 100 shots equally well aimed at the center. We shall find three important facts associated with the distribution of the bullets:

1. Some bullets have struck above the center, while about an equal number have struck below.

2. The number of bullets striking near the target center is greater than the number striking in an equal area some distance from the center.

3. The number of bullets striking at a distance from the center is very small.

The last two facts may be expressed in another way. The probability that a bullet will strike near the center is great, while the probability that it will strike at some distance from the center is small. The probability that a bullet will strike outside the target is very small indeed.

We see, then, that small deviations from the center are very likely to happen, larger deviations less likely to happen, and very large deviations very unlikely to happen.

Deviations.	Probability of Happening.
Small	Large.
Larger	Smaller.
Large	Small.

That is, the probability of a deviation varies inversely as the size of that deviation. In other words, the probability of a deviation or error is a function (f) of that error. Let y denote the probability and x the error; we may express this relation in the form—

$$y = f(x).$$

If several equally good observations are made upon an unknown quantity, we are justified in saying that the mean of the results is the most likely or the most probable. The individual results, however, will differ from this mean, and these differences are called residuals. If the mean were the true value, these differences or residuals would be errors.

Let $O_1, O_2, O_3 \ldots O_n$ denote values of observation.
M " mean value.
T " true value.
$r_1, r_2, r_3 \ldots r_n$ " residuals.
$x_1, x_2, x \ldots x_n$ " errors.

Then $(O_1 - M) = r_1$, $(O_2 - M) = r_2$, $(O_2 - M) = r_2 \ldots (O_n - M) = r_n$.
$(O_1 - T) = x_1$, $(O_2 - T) = x_2$, $(O_3 - T) = x_3 \ldots (O_n - T) = x_n$.

Now the errors are some plus and some minus, hence their sum will cancel:

Therefore, $(O_1—T) + (O_2—T) + (O_3—T) + \ldots\ldots\ldots\ldots\ldots\ldots (O_n—T) = O.$

From above we have $y_1 = f(x)_1.$

$y_2 = f(x_2).$

$y_3 = f(x_3).$

$\ldots\ldots\ldots$

$y_n = f(x_n).$

Multiplying $y_1, y_2, y_3 \ldots y_n = f(x_1)\, f(x_2)\, f(x_3) \ldots\ldots\ldots\ldots\ldots\ldots f(x_n) = P.$ (say).

Now the most probable value of the unknown quantity will be such that P is a maximum.

Taking logarithms, we have:

$$\text{Log}P = \text{log}f(x_1) + \text{log}f(x_2) + \text{log}f(x_3) + \ldots\ldots\ldots\ldots\ldots\ldots \text{log}f(x_n).$$

Differentiate.

$$\frac{d\text{log}P}{dT} = \frac{d\text{log}f(x_1)dx_1}{dx_1\ dT} + \frac{d\text{log}f(x_2)dx_2}{dx_2\ dT} + \frac{d\text{log}f(x_3)dx_3}{dx_3\ dT} + \ldots \frac{d\text{log}f(x_n)dx_n}{dx_n\ dT} = O$$

$$\text{and } \frac{dx_1}{dT} = \frac{dx_2}{dT} = \frac{dx_3}{dT} \ldots\ldots\ldots \frac{dx_n}{dT} = -1$$

Substituting,

$$\frac{d\text{log}f(O_1—T)}{d(O_1—T)} + \frac{d\text{log}f(O_2—T)}{d(O_2—T)} + \frac{d\text{log}f(O_3—T)}{d(O_3—T)} + \ldots\ldots\ldots \frac{d\text{log}f(O_n—T)}{d(O_n—T)} = O$$

Or,

$$\frac{(O_1—T)d\text{log}f(O_1—T)}{(O_1—T)d(O_1—T)} + \frac{(O_2—T)d\text{log}f(O_2—T)}{(O_2—T)d(O_2—T)} + \ldots\ldots\ldots \frac{(O_n—T)d\text{log}f(O_n—T)}{(O_n—T)d(O_n—T)} = O$$

and from above $(O_1—T) + (O_2—T) + (O_3—T) + \ldots\ldots\ldots\ldots (O_n—T) = O.$

Hence $\frac{d\text{log}f(O_1—T)}{(O_1—T)d(O_1—T)} = \frac{d\text{log}f(O_2—T)}{(O_2—T)d(O_2—T)} = \frac{d\text{log}f(O_n—T)}{(O_n—T)d(O_n—T)} = \ldots\ldots\ldots k$ (say).

Hence $d\text{log}f(x) = kxd(x).$

$\text{log}f(x) = \frac{1}{2}kx^2 + \text{log}e.$

$f(x) = ce^{\frac{1}{2}k2}$

As x increases f(x) decreases.

Hence k must be negative.

Putting $\frac{1}{2}k = —h^2$ we have—

$f(x) = ce^{—h^2x^2}$

$\int_{—\infty}^{\infty} ce^{—h^2x^2}dx = 1.$

Putting $hx = t$ we have—

$hdx = dt.$

Hence $\int_{—\infty}^{\infty} \frac{ce^{—t^2}\, dt}{h} = 1.$

Now $\int_{—\infty}^{\infty} e^{—t^2}dt = \sqrt{\pi}$

Hence $\frac{c}{h}\sqrt{\pi} = 1$ or $c = \frac{h}{\sqrt{\pi}}$

Therefore, $f(x) = \frac{he^{—h^2x^2}}{\sqrt{\pi}}$

Substituting in the equation for P we have—

$$P = \left(\frac{h}{\sqrt{\pi}}\right)^n e^{-h^2(x^2_1+x^2_2+x^2_3+\ldots\ldots\ldots\ldots x^2n)}$$

From which we see that, as P increases, the exponent of e diminishes, or P will be a maximum when $x^2_1 + x^2_2 + x^2_3 + x..x_n{}^2$ is a minimum.

Hence, the most probable value of the unknown quantity is that which makes the sum of the squares of the residuals a minimum.

Probable Error.

The probable error is such a quantity that the chance of an error happening greater than this specified error is equal to the chance of an error happening less.

If we toss a coin into the air, it is certain that it will fall either heads or tails up. This certainty is usually expressed by the unit 1. Now it is an even wager that it will fall either heads or tails. The probability that it will fall heads we express by the fraction $\frac{1}{2}$.

If p denote the probable error, then the probability that an error will happen greater than r is $\frac{1}{2}$, and that an error will happen less than r is also $\frac{1}{2}$.

Hence we have—

$$\frac{2h}{\sqrt{\pi}}\int_0^p e^{-h^2x^2}dx = \tfrac{1}{2};\ \text{or,}\ \frac{2}{\sqrt{\pi}}\int_0^{hp} e^{-t^2}dt = \tfrac{1}{2}$$

Integrating we have $hp = 0.477$.

Mean Error.

The mean error is a quantity whose square is the mean of the squares of the individual errors.

Let $x_1, x_2, x_3 \ldots\ldots\ldots\ldots x_n$ denote errors which occur.
" $f(x_1), f(x_2), f(x_3) \ldots\ldots\ldots\ldots f(x)_n$ denote respective probabilities.
" m.....denote mean error.
" n.....denote number of observations.

$$\text{Then } m^2 = \frac{2nf(x_1)x^2,\ 2nf(x_2)^2x_2 + 2nf(x_3)x^2_3 + \ldots\ldots\ldots 2nf(x_n)x^2_n}{n}$$

$$= 2\int_o^\infty f(x)x^2.\ dx$$

$$\text{whence } m^2 = 2\int_o^\infty \frac{h}{\sqrt{\pi}}\ x^2\ e^{-h^2x^2}dx = \frac{1}{2h^2},\ \text{and}\ P = \frac{.477}{h}$$

or $m = 1.483p$, or $p = 0.6745m$

Hence P has a fixed numerical relation to m, so that when m is obtained, we get the value of p directly.

DETERMINATION OF MEAN ERROR.

As before let $O_1, O_2, O_3 \ldots O_n$ denote values of observations.
$M \ldots$ " mean value.
$r_1, r_2, r_3 \ldots r_n$ " value of residuals.
$T \ldots$ " true value.
$d \ldots$ " error of mean value.
$x_1, x_2, x_3 \ldots x_n$ " true errors.
Then $x_1 = r_1 - d$, $x_2 = r_2 - d$, $x_3 = r_3 - d \ldots$ $x_n = r_n - d$.

Squaring each side of each equation we have—

$$\text{Sum of } (x^2) = \text{sum of } (r^2) + \text{sum of } (d^2).$$

The products "rd," being some plus and some minus, will cancel.

Now $nd^2 = \frac{nm^2}{n}$, nearly. And $nm^2 = \text{sum of } (x^2)$.

Hence $nm^2 = \text{sum of } (r^2) + m^2$.

$$m^2(n-1) = \text{sum of } (r^2).$$

Hence $m = \sqrt{\frac{\text{sum}(r^2)}{(n-1)}}$ $\qquad p = .6745\sqrt{\frac{\text{sum}(r^2)}{(n-1)}}$

Looking at this equation we see that m varies with the value of the sum of (r^2), n being constant. If many of the residuals are large, we naturally conclude that m will also be large. If the residuals are uniformly small, it follows that m will also be small. Now, when the residuals are small, we know that the mean value of the observations is in close accordance with the individual observations, and we pronounce the result as satisfactory. We are justified, then, in saying that the mean error is a criterion of the value of the work performed.

In applying this expression to practical observations we are met with the terms n and sum of (r^2). Now n denotes the number of observations and is known, while r denotes the residual, or, as we have defined it, the difference between the mean of the observations and the individual observation. In the following figures the opsonic indices are given after the equation sign. The mean of these indices is 100. In the second column are found the residuals. In the third column are found the squares of these residuals. The sum of these squares is 18855. The number of individual observations happens to be an even hundred. Hence we have—

$$\sqrt{\frac{\text{Sum of } (r^2)}{(n-1)}} = \sqrt{\frac{18855}{99}} = \sqrt{190 \text{ nearly}, = \pm 14 \text{ nearly}, = m},$$

which Reyn and Kjer-Petersen call μ, or "standard deviation."

To most minds the mean error would suggest that value which would be the mean of the errors. In developing the theory, however, we have seen that the most probable value of the unknown quantity is such that the sum of the squares of the residuals is a minimum. This is the keynote

of the problem. Now, if we must consider the squares of residuals, it follows that the mean of these squares should itself be a square. Hence the definition of mean error as given above.

Now the probable error has a fixed numerical relationship with the mean error:

$$\begin{aligned} \text{From above } p &= .6745m. \\ &= .6745(\pm 14). \\ &= \pm 9 \end{aligned}$$

We see that either of these errors may be used as a criterion of our work, provided we consistently use the one we prefer to adopt.

In all work where an unknown quantity is sought the observer should not allow a possible known value to influence or bias his observations. The inexperienced observer, as well as the overanxious observer, is apt to discard results which appear to be abnormal. Unless some good reason can be given for believing the observation to be influenced by poor adjustment or poor technic, the result should usually be retained, even though the error be large. That result which gives a large error may be nearer the true value than it appears, so that if we throw this individual result out, we are discarding a result which should have its controlling influence.

In arriving at figures which go to show the value of the opsonic method as a guide to the use of tuberculin, two essentially different sources may cause the variation in figures:

1. The control serum itself may vary.

2. The method or technic by which these figures are obtained may be at fault.

The mean error of an individual observation of our work is obtained from the following 100 separate tests of a healthy normal serum.

MEAN ERROR OPSONIC INDICES.

				Residual or Error.	Squared Residual.
	Set 1: Mean Phagocytic index, 94.				
1	Opsonic index	T_1	95/94 = 101	.01	0.0001
2	"	T_2	92/94 = 98	.02	0.0004
3	"	T_3	101/94 = 107	.07	0.0049
4	"	T_4	87/94 = 93	.07	0.0049
	Set 2: Phagocytic index, 74.				
5	Opsonic index	T_1	74/74 = 100	.00	0.0000
6	"	T_2	94/74 = 127	.27	0.0729
7	"	T_3	57/74 = 77	.23	0.0529
8	"	T_4	69/74 = 93	.07	0.0049
	Set 3: Phagocytic index, 40.				
9	Opsonic index	T_1	50/40 = 125	.25	0.0625
10	"	T_2	28/40 = 70	.30	0.0900
11	"	T_3	39/40 = 98	.02	0.0004
12	"	T_4	43/40 = 107	.07	0.0049

MEAN ERROR OPSONIC INDICES.—(*Continued.*)

					Residual or Error.	Squared Residual.
	Set 4: Phagocytic index, 52.					
13	Opsonic index	T_1	56/52	= 108	.08	0.0064
14	" "	T_2	55/52	= 106	.06	0.0036
15	" "	T_3	42/52	= 81	.19	0.0361
16	" "	T_4	57/52	= 110	.10	0.0100
	Set 5: Phagocytic index, 53.					
17	Opsonic index	T_1	53/53	= 100	.00	0.0000
18	" "	T_2	57/53	= 108	.08	0.0064
19	" "	T_3	49/53	= 92	.08	0.0064
20	" "	T_4	51/53	= 96	.04	0.0016
21	" "	T_5	55/53	= 104	.04	0.0016
	Set 6: Phagocytic index, 51.					
22	Opsonic index	T_1	49/51	= 96	.04	0.0016
23	" "	T_2	49/51	= 96	.04	0.0016
24	" "	T_3	47/51	= 92	.08	0.0064
25	" "	T_4	58/51	= 114	.14	0.0196
	Set 7: Phagocytic index, 73.					
26	Opsonic index	T_1	72/73	= 99	.01	0.0001
27	" "	T_2	77/73	= 105	.06	0.0036
28	" "	T_3	67/73	= 92	.08	0.0064
29	" "	T_4	71/73	= 97	.03	0.0009
30	" "	T_5	76/73	= 104	.04	0.0016
31	" "	T_6	76/73	= 104	.04	0.0016
	Set 8: Phagocytic index, 71.					
32	Opsonic index	T_1	75/71	= 106	.06	0.0036
33	" "	T_2	70/71	= 99	.01	0.0001
34	" "	T_3	82/71	= 115	.15	0.0225
35	" "	T_4	67/71	= 94	.06	0.0036
36	" "	T_5	59/71	= 83	.17	0.0289
	Set 9: Phagocytic index, 57.					
37	Opsonic index	T_1	55/57	= 96	.04	0.0016
38	" "	T_2	57/57	= 100	.00	0.0000
39	" "	T_3	61/57	= 107	.07	0.0049
40	" "	T_4	56/57	= 98	.02	0.0004
41	" "	T_5	54/57	= 95	.05	0.0025
	Set 10: Phagocytic index, 58.					
42	Opsonic index	T_1	64/58	= 110	.10	0.0100
43	" "	T_2	49/58	= 84	.16	0.0256
44	" "	T_3	59/58	= 102	.02	0.0004
45	" "	T_4	49/58	= 84	.16	0.0256
46	" "	T_5	67/58	= 116	.16	0.0256
	Set 11: Phagocytic index, 116.					
47	Opsonic index	T_1	135/116	= 116	.16	0.0256
48	" "	T_2	135/116	= 116	.16	0.0256
49	" "	T_3	95/116	= 82	.18	0.0324
50	" "	T_4	119/116	= 103	.03	0.0009
51	" "	T_5	110/116	= 95	.05	0.0025
52	" "	T_6	105/116	= 90	.10	0.0100
	Set 12: Phagocytic index, 86.					
53	Opsonic index	T_1	85/86	= 99	.01	0.0001
54	" "	T_2	80/86	= 93	.07	0.0049
55	" "	T_3	91/86	= 106	.06	0.0036
56	" "	T_4	86/86	= 100	.00	0.0000
	Set 13: Phagocytic index, 50.					
57	Opsonic index	T_1	59/50	= 118	.18	0.0324
58	" "	T_2	55/50	= 110	.10	0.0100
59	" "	T_3	43/50	= 86	.14	0.0196
60	" "	T_4	45/50	= 90	.10	0.0100

MEAN ERROR OPSONIC INDICES.—(*Continued.*)

		Residual or Error.	Squared Residual.
	Set 14: Phagocytic index, 95.		
61	Opsonic index T_1 112/95 = 118	.18	0.0324
62	" " T_2 96/95 = 101	.01	0.0001
63	" " T_3 89/95 = 94	.06	0.0036
64	" " T_4 81/95 = 85	.15	0.0225
	Set 15: Phagocytic index, 54.		
65	Opsonic index T_1 59/54 = 109	.09	0.0081
66	" " T_2 49/54 = 91	.09	0.0081
	Set 16: Phagocytic index, 155.		
67	Opsonic index T_1 101/155 = 65	.35	0.1225
68	" " T_2 161/155 = 104	.04	0.0016
69	" " T_3 180/155 = 116	.16	0.0256
70	" " T_4 163/155 = 105	.05	0.0025
71	" " T_5 160/155 = 103	.03	0.0009
72	" " T_6 163/155 = 105	.05	0.0025
	Set 17: Phagocytic index, 146.		
73	Opsonic index T_1 91/146 = 62	.38	0.1444
74	" " T_2 119/146 = 81	.19	0.0361
75	" " T_3 193/146 = 132	.32	0.1024
76	" " T_4 164/146 = 112	.12	0.0144
77	" " T_5 166/146 = 114	.14	0.0196
78	" " T_6 143/146 = 98	.02	0.0004
	Set 18: Phagocytic index, 40.		
79	Opsonic index T_1 38/40 = 95	.05	0.0025
80	" " T_2 39/40 = 98	.02	0.0004
81	" " T_3 32/40 = 80	.20	0.0400
82	" " T_4 50/40 = 125	.25	0.0625
	Set 19: Phagocytic index, 31.		
83	Opsonic index T_1 32/31 = 103	.03	0.0009
84	" " T_2 31/31 = 100	.00	0.0000
85	" " T_3 29/31 = 94	.06	0.0036
	Set 20: Phagocytic index, 31.		
86	Opsonic index T_1 25/31 = 81	.19	0.0361
87	" " T_2 30/31 = 97	.03	0.0009
88	" " T_3 38/31 = 123	.23	0.0529
	Set 21: Phagocytic index, 26.		
89	Opsonic index T_1 30/26 = 115	.15	0.0225
90	" " T_2 19/26 = 73	.27	0.0729
91	" " T_3 29/26 = 112	.12	0.0144
	Set 22: Phagocytic index, 120.		
92	Opsonic index T_1 130/120 = 108	.08	0.0064
93	" " T_2 103/120 = 86	.14	0.0196
94	" " T_3 126/120 = 105	.05	0.0025
	Set 23: Phagocytic index, 101.		
95	Opsonic index T_1 84/101 = 83	.17	0.0289
96	" " T_2 94/101 = 93	.07	0.0049
97	" " T_3 70/101 = 69	.31	0.0961
98	" " T_4 127/101 = 126	.26	0.0676
99	" " T_5 106/101 = 105	.05	0.0025
100	" " T_6 124/101 = 123	.23	0.0529

Sum of squares = 18855

$$\frac{18855}{99} = 190$$

Square root of 190 = 14 +
Mean error = $\pm 14 = \mu$

		Practical.	Mathematical.
7 = ½ μ	No. of errors from ..... 0—07	50	38.3
14 = μ	.....00—14	69	68.3
28 = 2 μ	.....00—28	93	95.4
42 = 3 μ	.....00—42	100	99.7
56 = 4 μ	.....00—56	100	99.9

The above table shows that 50 of the 100 residuals are between +7 and —7. If we compute the indices to the decimal figure, we shall find but 46 residuals between these limits.

If our observations had been infinite in number, we should expect 38.3 per cent. between these limits. Though the theoretical number does not agree exactly with the practical, the residuals are fairly well distributed between the limits 7. Five of these residuals equal 0; five equal 1; six equal 2; five equal 3; eight equal 4; seven equal 5; seven equal 6.

The actual number below our standard deviation is 69, which corresponds very closely with the theoretical 68.3.

It may be of interest to compare our standard deviation with that of other writers:

Bulloch reports a mean error of.....09
Peterson reports a mean error of.....19
Urwick reports a mean error of 11
Lawson and Stewart reports a mean error of.....13
Fleming reports a mean error of.....10
Shaw reports a mean error of.....19
Kinghorn and Twichell report a mean error of 14

Value of the Tuberculo-opsonic Index as a Control to Tuberculin Treatment in Pulmonary Tuberculosis.

Our chief objects in making tuberculo-opsonic tests on phthisical patients that were being treated with tuberculin were to endeavor to get a general view of the effect of the doses on the opsonic indices of the patients, and to see if we should have to modify our present methods of giving tuberculin from the information obtained. The tuberculins used were Koch's old tuberculin, the bouillon filtrate (as described by Denys), and Koch's bacillen emulsion. The method of administering the tuberculin was according to the slow or progressive method, and we followed the directions given by Dr. E. L. Trudeau in the American Journal of the Medical Sciences, June, 1907. The doses were given at intervals of from three to four days. When large doses were reached, the intervals were lengthened. We did not follow Professor Wright's methods, and control the doses by the opsonic index, but critically examined the effect of the doses on the opsonic index. Our patients were all in good physical condition and were without fever. In most of them the opsonic index was tested more or less frequently throughout

the whole course of treatment. For instance, it was tested each day for several weeks, then an interval of perhaps a month passed, and the index was again tested each day for several weeks. In this way a continuous immunity curve was obtained.

Do Injections of Tuberculin Raise the Opsonic Index?

It is interesting to know whether injections of tuberculin to phthisical or healthy persons will raise the opsonic index. To test this we examined thirteen tuberculous and three healthy persons. The three healthy persons failed to react to the tuberculin test. The average opsonic index of the first half of the total number of tests for each individual was compared with the average opsonic index of the second half. Of thirteen tuberculous patients, the opsonic index was raised in eleven and diminished in two. It was raised in two of the healthy persons and diminished in one. It seems evident, therefore, that tuberculin injections will raise the tuberculo-opsonic index.

TABLE.

Case Tub. Cases.	Number of Tuberculo-Opsonic Tests.	Average Opsonic Index of First Half of Tests.	Average Opsonic Index of Second Half of Tests.	Gain or Loss.
Mrs. W.	22	0.90	1.05	15 points gain
G. P.	60	0.99	1.17	18 " "
E. T.	26	0.98	1.03	5 " "
J. P.	42	0.90	0.94	4 " "
R. B.	22	0.91	0.99	8 " "
L. E.	16	0.85	1.08	23 " "
F. W.	60	0.94	1.05	11 " "
K.	29	0.88	1.06	18 " "
H.	15	1.04	1.14	10 " "
C.	11	1.19	1.79	60 " "
M.	12	1.11	1.24	13 " "
J. H.	20	0.98	0.75	23 " loss
E. G.	22	0.98	0.89	9 " "
Healthy.	..			
R. T.	12	1.26	1.43	17 " gain
McL.	24	1.06	1.14	8 " "
B. W.	26	0.95	0.89	6 " loss

In passing we might mention the result of treatment on these cases. Mrs. W. had a discharging sinus in the abdomen as a result of operation for tuberculous disease of the ovaries. She was given not only bacillen emulsion, but also a vaccine obtained from a coccus isolated from the discharge. The doses were given at variable intervals—usually seven to ten days. Her general health improved markedly, and the discharge was very much lessened. Of the remaining eleven tuberculous cases, two received tuberculin

injections for test purposes and reacted; the remaining cases all received tuberculin according to the slowly progressive method; seven were advanced and two were incipient. The two incipient cases became apparently cured; one of the advanced cases became apparently cured, and the remaining all markedly improved, one of them losing the tubercle bacilli from the sputum, but still having slight cough and expectoration. Most of the advanced cases had been previously either stationary or slowly failing. The opsonic index of one of the advanced cases was very much lowered by treatment. This patient, however, became apparently cured. The number of cases tested was too small to draw any conclusion as to whether those cases improved most whose opsonic index increased most. In ten of the cases the index was maintained at or above normal during the latter half of the tests.

Negative Phases.

Does a negative phase regularly occur after a tuberculin injection?

It is generally believed that the injection of a therapeutic dose of a vaccine, and, therefore, of tuberculin, is invariably followed by a fall in the opsonic index lasting from three days to a variable time—sometimes several weeks. This period of low opsonic index is known as the "negative phase," and is followed by a period of high opsonic index which is known as the "positive phase," which lasts for a variable number of days, after which the index returns to about its original level. The whole cycle is believed by many of Wright's followers to be invariable, and it is not out of place to state his present view of what does occur. Wright now says, when, instead of testing the blood after inoculation at intervals of from a week to ten days, the blood is tested from day to day, there generally occurs a depression. The rise which is achieved by inoculation is only a transient one, and generally declines after an interval, sometimes sinking away until it reaches the point at a level only a little above the original base line. Where more frequent, and in particular where earlier blood examinations are made, another practically constant feature is seen. This is the transient initial rise preceding the negative phase. These changes are not universally conformed to. Where a dose of vaccine is given which is not just sufficient to produce a result, the negative phase is elided, and there is registered only a positive phase. The curve in such a case neither rises so high, nor does it maintain itself so long above the base line, as when a larger dose of vaccine has been given.

Where an excessive dose of vaccine is administered,—that is, a dose which produces severe constitutional symptoms,—the negative phase is accentuated and prolonged. Where the dose of vaccine is immoderately large, the negative phase may last for weeks. Our tests corroborate only

some of these features mentioned by Wright. For instance, we have investigated the effect of too large a dose of tuberculin; that is to say, a dose which caused reaction accompanied by constitutional disturbance and fever. Of 8 definite tuberculin reactions produced on eight different patients, in 4 there was a definite positive phase, and in 4 a definite negative phase, immediately following the injection, as indicated by the opsonic index. Of the negative phases, one lasted one day, two lasted two days, and one lasted three days. We, therefore, cannot agree with Professor Wright that an excessive dose of vaccine produces a negative phase which is accentuated and prolonged.

Following almost all tuberculin doses, we observed a change in the opsonic index from what it was just before the injection. In 88 series of tests (which were composed of over 400 separate opsonic tests) in which we followed the opsonic index each day from one injection to the next, we found immediately following the dose there was a well-defined negative phase in 45 tests, or 51 per cent., and a well-defined positive phase in 43 tests, or 49 per cent. With some patients the tests showed almost entirely first negative, then positive, phases; with other patients exactly the reverse occurred: there were few or no negative phases, but only positive phases. We regard as positive or negative phase the opsonic index on the day following the dose of tuberculin.

From our figures the numbers of negative and positive phases immediately following doses of tuberculin are practically equal.

It is evident tuberculin injections, whether small or large, change the opsonic index either positively or negatively, and that negative phases do not invariably follow tuberculin doses, but occur about as often as positive phases.

How Long do Positive and Negative Phases Last?

As we gave our dose at intervals of three to four days for the small doses, and at longer intervals for the larger ones, in many instances the negative and positive phases had not ceased before the next dose of tuberculin was given. We here only record those phases immediately following the injections which had definitely ceased when the next injection was made. We find that 24 of the 45 negative phases had entirely ceased within five days, and 20 had ceased within four days. As we made 88 separate and complete series of tests from day to day, we thus find that in only 21 series of the 45 negative phases, or in 24 per cent. of cases, does a negative phase last longer than five days, and in 25 series of the 45 negative phases, or 28 per cent., does it last longer than four days, and in 26 of the 45, or 30 per cent., does it last longer than three days. Roughly speaking, therefore, it appears that in giving tuberculin at intervals of three to four days, and according to the

TABLE SHOWING THE NUMBER OF NEGATIVE AND POSITIVE PHASES OF EACH CASE.

Case.	Total Number of Series of Tests.	Range of Dose of Tuberculin.	Number of Negative Phases.	Number of Positive Phases.
1. J. P.....	8	0.008 to 0.550 gm. old tuberculin.	2	6
2. E. T.....	5	0.0001 to 0.0025 milligram bouillon filtrate.	0	5
3. G. P.....	15	0.001 to 0.035 gm. old tuberculin.	7	8
4. C.....	2	0.0005 to 0.002 gm. old tuberculin.	1	1
5. D.....	1	0.001 gm. old tuberculin.	0	1
6. B.....	7	0.0006 to 0.0017 gm. old tuberculin.	6	1
7. L. E.....	2	0.0005 to 0.002 gm. old tuberculin.	0	2
8. W.....	15	0.0012 to 0.204 gm. old tuberculin.	8	7
9. Mrs. F.....	1	0.0005 gm. old tuberculin.	..	1
10. K.....	9	0.001 to 0.002 gm. old tuberculin and 0.00002 to 0.0005 gm. bovine filtrate.	7	2
11. H.....	4	0.029 to 0.129 gm. old tuberculin.	2	2
12. D.....	1	0.001 gm. old tuberculin.	0	1
13. G.....	4	0.248 to 0.380 gm. old tuberculin.	3	1
14. McN.....	2	0.148 to 0.162 gm. old tuberculin.	2	0
15. Has.....	4	0.274 to 0.344 gm. old tuberculin.	1	3
16. Mont.....	2	0.0005 to 0.002 gm. old tuberculin.	2	0
17. R.....	1	1.45 milligram bacillen emulsion.	1	0
18. M.....	2	0.0014 to 0.0015 milligram bacillen emulsion.	1	1
19. A.....	3	1.17 to 1.61 milligram bacillen emulsion.	2	1
	88		45 = 51 per cent.	43 = 49 per cent.

progressive method, in about 70 per cent. of cases the injections are given when there has been either no negative phase, or if there were, it has already ceased, and that if we give doses at intervals of five days, in 75 per cent. of cases the injections are given when no negative phase exists. If, therefore, the opsonic index, in the negative phase, represents a depressed condition of the patient, it would seem as if occasionally the intervals between doses should be rather longer than they are at present.

We found a positive phase to occur 43 times in the 88 series of tests,

i. e., 49 per cent. One fact seems manifest, that with intervals of three to four days, in a considerable number of cases the opsonic index has not regained its normal by the time the next dose is given.

TABLE SHOWING NEGATIVE AND POSITIVE PHASES WHICH HAD CEASED WHEN THE FOLLOWING DOSE WAS GIVEN.

Case.	Negative Phase.	Length in Days of Negative Phase.	Positive Phase.	Length in Days of Positive Phase.
J. P.....	1. 1.	1. 1.	1. 1. 1.	2. 1. 2.
E. T.....	0.	0.	1. 1. 1. 1.	2. 4. 2. 4.
G. P.....	1. 1. 1. 1. 1. 1.	2. 1. 1. 5. 1. 7.	1. 1. 1. 1. 1.	2. 1. 2. 1. 2.
B.	1. 1.	3. 3.	1.	1.
W.	1. 1. 1.	3. 2. 1.	1. 1. 1. 1.	1. 2. 2. 2.
K.	1. 1.	1. 2.	1.	2.
J. H.....			1. 1.	1. 1.
E. G.....	1. 1. 1	2. 5. 6.	..	..
L. M.....	1. 1.	1. 3.	..	..
Has.....	1.	2.	1. 1. 1.	1. 1. 1.
Mont.....	1. 1.	5. 2.	..	..
R.	1.	4.	..	..
C.	1.	1.	1.	2.
Mil.....	1.	5.	..	..
L. E.....	0.	..	1. 1.	1. 1.
Mrs. F.....	..	..	1.	2.
	26		26	

Do Tuberculin Injections Still Further Depress Negative Phases?

Until Professor Wright modified this point, it was one of the principles of the opsonic index that a dose of vaccine should not be given while the opsonic index is in the negative phase, because it was held that the index would be depressed still further. We have investigated all our opsonic tests where the dose of tuberculin was given while the index was considerably below its average normal. In only 3 out of 20 such tests was the opsonic index still further lowered; in the remaining 17 tests a positive phase set in. Wright has found the same thing to occur. In a foot-note on page 493 of the Lancet, August 24, 1907, he says: "Where by inadvertence an excessive dose of vaccine has been administered, it is unnecessary indefinitely to await the return of the bacteriotropic pressure to the normal. In such a case the desired rise can practically always be obtained by reinoculating, as soon as all constitutional symptoms have disappeared, with a minimal dose of vaccine."

At this point it is interesting to investigate for a moment how soon the evidence of immunity will show itself in the blood after a dose of vaccine, and at what intervals injections of vaccines may safely be given. The traditional view is that a period of ten days is always required for the estab-

lishment of active immunity. R. Koch, for instance, found in patients that were being treated with bacillen emulsion, agglutination to be at its height in from eight to twelve days. Pasteur regarded ten days as necessary to establish active immunity, and largely owing to him it has become the routine to make test inoculations at ten-day intervals. Wright quotes Haffkine as being the first to claim that a condition of immunity was achieved already, within twenty-four hours after the inoculation of a vaccine. Haffkine put forward this claim in connection with his plague vaccine. Some years later, the matter in the mean time having been advanced a step further by the publication, under Haffkine's auspices, of evidence pointing to the successful inoculation of patients who were already in the incubation period of plague, Sir Almroth Wright obtained, in the course of a study of the changes effected by antityphoid inoculation in the bactericidal power, evidence of development of increased bactericidal power in the blood on the day subsequent to the inoculation of moderate doses of antityphoid vaccine. He obtained also, in connection with his first therapeutic inoculations of staphylococcus vaccine, evidence of increased phagocytic response on the day subsequent to inoculation. Wright has also obtained conclusive evidence of an increase of the opsonic power of the blood within an hour after the inoculation of tubercle vaccine in an infection of the eye. Also in furunculosis by inoculations of staphylococcus vaccine he obtained trustworthy evidence of clinical improvement within an hour after inoculation.

If the negative phase represents a depressed condition, we think we have shown from our tests that this phase lasts a very much shorter time and occurs much less often than is generally supposed. In other words, it would seem as though we have in our tests definite evidence that immunity is well demonstrated in three to four days, because by this time in 70 per cent. of cases the negative phase has either definitely ceased or has not occurred. Time will tell whether a greater immunizing response will be obtained by lengthening this interval. At the present time we think we can say that this interval is at least a safe one.

In connection with the value of the tuberculo-opsonic test as a control to tuberculin treatment in pulmonary tuberculosis we must consider whether the test is practical. With a good technic and working without interruptions it requires about two hours to make and stain from four to six tests. It then requires at least two hours to count these. It is often necessary to give four or five tuberculin injections each day. When a large number of patients are receiving injections it is, therefore, impossible to follow the opsonic indices of all these patients from day to day without a staff of trained opsonists. Wright overcomes this difficulty by making tests at considerable intervals, and not from day to day. In this way he finds out if the index

is still in the negative phase, and if so, he waits longer before giving the next dose of vaccine. His knowledge of the duration of past positive phases permits him to give his dose with fair accuracy without making daily tests. This knowledge, however, was obtained by making daily tests at the outset of his work. If the test represents the immunity of the patient, Wright's claim seems justified to give doses during the decline of the positive phase.

We think, however, far too much reliance is placed by many workers on the value of individual scattered tests as guides to the next dose, but at the same time consider that moderate intervals of dosage seem reasonable. Dr. D. Lloyd Smith and his coworkers have reached this same conclusion, and state that in pulmonary tuberculosis "one cannot determine on the result of one estimation of the index whether an injection of tuberculin should be given or not."

From our work we think we have proved that the tuberculo-opsonic index is raised by injections of tuberculin; that negative and positive phases occur with about equal frequency after injections; that when we give injections at intervals of three or four days, in about 70 per cent. of cases the injections are given when the negative phase has either already ceased or has not occurred; that when an injection is made during a negative phase, the index is rarely depressed still further, but that a positive phase at once sets in. In answering our question as to the value of the test to control tuberculin injections, we think that while it is quite impractical and impossible to use it each day on each patient, yet from our work it has showed itself to be of definite value with regard to the spacing of doses, namely, that in the vast majority of cases the positive and negative phases immediately following the injections have ceased within three or four days.

We cannot, however, overlook the fact that the opsonic test is a difficult one. Comparatively few workers have attained to a technic which is reliable. Most workers who have attempted to master the technic have failed. This fact limits the value of the test. To those who have mastered the technic the length of time necessary to make tests seems out of all proportion to the value of the test. Where several injections of tuberculin are given each day, it is impossible to make opsonic tests on all. We think scattered individual tests on patients do not give sufficiently accurate information. We also think there is not sufficient uniformity in the knowledge obtained from even individual series of tests. The variations in the results following doses of tuberculin are very great, and, as a result, Wright has had to modify his original statements to a considerable extent. Wright has described great underlying principles of changes which follow doses of vaccine, but the variations to these changes are extremely frequent and need too much explanation to be of value as guides. We regard the tuberculo-opsonic test as one of fair accuracy, but question its value in pul-

monary tuberculosis. We do not, however, wish to detract from the value of the principles of vaccination which Wright has described, and, at the same time, wish to state our appreciation of the great influence he has produced in directing attention to the great value of tuberculin and other vaccines.

In the progressive method of using tuberculin, we begin with much smaller doses than does Wright, but increase gradually to much larger ones. Our object is to give our patient tuberculin immunity and not to keep his opsonic index high. Time will decide which method is to be employed. We feel, however, that Wright has drawn attention by his opsonic index to changes which occur after a dose of tuberculin and other vaccines, and think the progressive method will be somewhat modified by his work, especially by lengthening the space between doses, particularly in patients with a feeble physique, and by giving somewhat smaller doses to such patients. In our judgment it would seem of much greater importance to attain to large doses of a vaccine, provided the patient were doing well, than merely to keep his opsonic index at a high level by small doses.

REFERENCES.

1. "Observations on the Opsonic Index in Pulmonary Tuberculosis," by Drs. D. Lloyd Smith, J. A. D. Radcliffe, Douglas Elder, and Mr. Alan Croosley, B.A., The Lancet, July 18, 1908.
2. "A Lecture on the Principles of Vaccine Therapy," Sir A. E. Wright, The Lancet, August 17 and 24, 1907.
3. "Some Observations on the Opsonic Index, with Special Reference to the Accuracy of the Method and to Some of the Sources of Error," Alexander Fleming, Practitioner, May, 1908.

Die Genauigkeit des Tuberculo-Opsonic-Index und sein Wert als eine Kontrolle der Tuberkulinbehandlung bei Lungentuberkulose.—
(Kinghorn, Twichell, Carter, und Werry.)

Der Vortrag ist in zwei Teile geteilt. Der erste befasst sich mit der Genauigkeit des Tuberculo-Opsonic-Index, und der zweite mit dem Wert des Versuches als eine Kontrolle der Tuberkulinbehandlung bei Lungentuberkulose.

Um eine Schätzung des Genauigkeitsgrades ihrer Arbeit zu erhalten, machten sie in verschiedenen Zwischenräumen Kontrollversuche. Es wurden dreiundzwanzig Versuchsserien von einem gesunden Serum gemacht. Jede Serie bestand aus 4.35 besonderen Versuchen. In allen einhundert waren die Versuche von demselben Serum gemacht worden. Diese Versuche waren von drei verschiedenen Beobachtern gemacht worden, alle von derselben Genauigkeit. Der Zweck war, den hauptsächlichen Irrtum einer einzelnen Beobachtung herauszufinden. Die ganze Frage wird von einem

mathematischen Gesichtspunkte aus angegangen. Der Hauptirrtum einer einzelnen Beobachtung war als plus oder minus 14 befunden worden, so dass bei einem gegebenen Versuchsserum und bei einem feststehenden Normalserum ein Spielraum von plus oder minus 14 zugestanden werden muss.

Ihre hauptsächlichen Bestrebungen bei den tuberculo-opsonischen Versuchen an mit Tuberkulin behandelten phthisischen Patienten waren die Bestrebungen, einen allgemeinen Überblick über die Wirkung der Dosen auf die Opsonic-Indices der Patienten zu gewinnen, und zu sehen, ob sie ihre gegenwärtigen Methoden, Tuberkulin zu geben, nach den erhaltenen Aufschlüssen modifizieren sollten. Ihre Methode, Tuberkulin anzuwenden, war die langsame oder progressive Methode und sie folgten den von Dr. E. L. Trudeau gegebenen Vorschriften. Die Dosen wurden in Zwischenräumen von drei oder vier Tagen gegeben. Wenn grosse Dosen gegeben wurden, verlängerte man die Zwischenräume. Sie folgten nicht Prof. Wright's Methode, nach welcher die Dosen durch den Opsonic-Index kontrolliert werden, sondern untersuchten kritisch die Wirkung der Dosen auf den Opsonic-Index. Bei den meisten ihrer Patienten war der Index am Anfange und während des gänzlichen Verlaufes der Behandlung untersucht worden. Auf diese Weise hatte man eine fortlaufende Immunitätskurve erhalten. Aus ihrer Arbeit fühlen sie bewiesen zu haben, dass der Tuberculo-Opsonic-Index durch Tuberkulin-Injektionen gehoben werden kann; dass in einer Mehrzahl von Versuchen bestimmte negative Phasen vorkommen, welche von positiven Phasen gefolgt sind; dass, wenn sie Injektionen in Intervallen von 3 bis 4 Tagen gaben, ein Viertel der Dosen gegeben wurde, wenn der Opsonic-Index noch in der negativen Phase war; dass, wenn eine Injektion während einer negativen Phase gemacht wurde, der Index selten weiter herabgedrückt wurde, dass aber auf einmal eine positive Phase einsetzte; dass in nur neunzehn Prozent der Fälle die positive Phase nicht aufgehört hatte, bevor die nächste Injektion gegeben war, wenn der Zwischenraum drei und vier Tage betrug.

Sie denken, dass, während es ganz unpraktisch und unmöglich ist, den Versuch jeden Tag an jedem Patienten zu machen, sich trotzdem aus ihrer Arbeit der Versuch als von bestimmtem Werte gezeigt hat, mit Bezug auf die zeiträumliche Einteilung der Dosen; namentlich dass die Zwischenräume zwischen den Dosen gelegentlich bedeutend länger sein sollten, als drei bis vier Tage. Sie betrachten den Tuberculo-Opsonic Versuch als einen von annehmbarer Genauigkeit, denken aber, dass er von zweifelhaftem Werte ist, um Tuberkulin-Injektionen bei phthisischen Patienten zu kontrollieren. Sie denken, das Ziel der Tuberkulinbehandlung sei eher, Tuberkulin-Immunisation hervorzurufen, als hauptsächlich den Opsonic-Index auf einem hohen Niveau zu erhalten.

THE TUBERCULO-OPSONIC INDEX IN THE DIAGNOSIS AND TREATMENT OF TUBERCULOSIS.

By Mary C. Lincoln, M.D.,

Private Laboratory, Dr. L. L. McArthur and Dr. J. C. Hollister, St. Luke's Hospital, Chicago

After a season of trial of a new measure or implement it is valuable to gather together all data, to tabulate it, to learn what it signifies, and thus to crystallize or correct impressions previously formed. The opsonic index has been used as a therapeutic guide in the tuberculin treatment of tuberculosis carefully and consistently by some, spasmodically by others, with the result of a somewhat divided opinion as to its value.

I would like to present some results and conclusions drawn from a study of over 3000 of our opsonic index determinations made during a period of about eighteen months in the treatment of 50 cases of tuberculosis. The patients were largely cases of bone and joint tuberculosis; the balance included gland tuberculosis, tuberculosis of the genito-urinary tract, pulmonary tuberculosis, and tuberculosis of the skin. The plan was to treat as many cases as was consistent with careful work, and to make as many opsonic examinations of these cases as possible. Daily examinations were made in the few cases that could be kept under close observation for several months. The attempt was made to administer the tuberculin according to the range of the index. The rise of the index following an injection was to be noted should it occur, the fall watched, and at the proper time another injection given. The idea was to maintain the index by tuberculin as nearly as possible at or above normal. In practice the range was such that injections were given about every seven to ten days, although there were many examples of an interval of less than seven days or of two weeks or more. Tables and charts were made of the opsonic curve of each patient, with clinical observations, and were published in the Journal of Surgery, Gynecology, and Obstetrics of October, 1907.

From these tables I have selected 8 cases typical of the entire series of cases treated since then, and have tabulated the indices before treatment, the index previous to each injection, and the highest index after each injection. (See Table 1.) A detailed examination of the indices of each patient and a comparative study between the patients bring out three

patent facts. first, that a very large proportion of all the indices are nearly identical, differing from one another by only 0.2 or 0.3. Second, in nearly every case examples may be seen of a marked rise or fall of the index a few or many times during the course of the treatment. Third, in every case the opsonic index is much higher at times and averages higher after tuberculin treatment than before. This last observation gains added significance when the index of normal individuals, as followed over a corresponding period of time, was found to range from only 0.8 to 1.2. Bearing these three observations in mind, it is of paramount importance to learn what degree of difference in indices must be attributed to limitations in technic and what degree can be depended upon to mean a difference in the opsonin content of the blood.

The salient point is, is the opsonic index the same one would obtain on a second examination of the same serum? Furthermore, is it a quantitative measure of the opsonins?

There are several directions in which one may proceed to test the opsonic technic. The same serums may be reëxamined under the same and under varying conditions; the same slides may be reëxamined by the same and different individuals. Turning to our daily records of opsonic indices, the difference between the counts of each slide of the same normal or of the different normals used daily may be followed. Over a period of eighty days it was found that 13 per cent. of the slides gave identical counts; that 26 per cent. gave a difference of 0.1; that 22 per cent. gave a difference of 0.2; that 33 per cent. gave a difference of 0.3, 0.4, or 0.5, and that 6 per cent. gave a difference of 0.6—that is, about 40 per cent. of the slides which theoretically should have given practically the same count differed by 0.3 to 0.6. Again, out of a series of about 50 slides, including normals and patients counted by different individuals, somewhat the same proportion of variation results, about 30 per cent. differing by 0.2 to 0.6. (See Table 2.)

On the other hand, examination of the same serums under varying conditions is a means of testing the technic. Naturally, there is a greater variation in the index when different creams are used, since the element of the agglutination of the red blood-corpuscles by the agglutinins of the serum may come into play. The following table gives the comparison with ten different serums run against five different creams, showing that 40 per cent. of the opsonic indices of the same serum differed by 0.6. (See Table 3.)

The bacterial emulsion used in determining the index offers a fruitful field for variation in results. The preparation of a satisfactory emulsion is, in my opinion, the most important detail. It is absolutely essential to use an emulsion as free of bacterial clumps as it is possible to make one, and it is most practical to use one that is thick enough to average about one bacillus per leukocyte for the normal serum. Table 4 of indices of the same serums,

when run through with emulsions of different densities, shows how markedly the index can vary if the emulsion is either very thick or very thin.

Is the opsonic index a quantitative measure of opsonins? in other words, will dilution of the serum give a corresponding lowering of the index? Should this be true, a serum diluted twice should have an index of one-half that of the full strength serum, or the ratio between the two indices should be 2, and for a dilution of 4 should be 4, and so on. I have tabulated the results of this test on four different serums, diluting each respectively two times, four times, and ten times. It is evident from Table 5 that the opsonic index by no means follows the degree of dilution of the serum. With a dilution of the serum of one-half, the average ratio between the indices of the diluted and undiluted serums was found to be 1 to 1.2, instead of 1 to 2, with a dilution of one-fourth the average ratio was found to be 1 to 1.6 instead of 1 to 4, and with a dilution of one-tenth the average ratio was found to be 1 to 2.2 instead of 1 to 10. There are startling variations from this average in the case of each serum tested, but there is a certain progression toward a higher ratio as the dilution increases. It appears doubtful, however, if that progression proceeds according to any law. The opsonic index is then not a quantitative measure of opsonins.

After intelligent comparison of the indices as obtained on repeated examinations and under varying conditions, it is evident that, with our present technic, only differences of 0.5, 0.6, or more can be considered as meaning differences in the opsonin content of the blood. Returning to our observations on the indices in the course of the tuberculin treatment of patients, we find that we must look only at the high lights. The time of administering each individual dose of tuberculin and the size of the dose cannot be guided by a difference of 0.2, 0.3, or even 0.4 in the index. We are not even justified in saying there has been a rise or a fall in the index unless there is at least more than 0.4 or 0.5 difference. We may, however, judge whether there is some reaction to the tuberculin so far as the opsonins are concerned by examining the indices over a considerable period of time, and thus gain some information as to interval and size of dose. In view of the skill and time required in determining indices, and in view of the limited degree of its accuracy, it would appear to me that the practical value of it as a therapeutic guide is much limited.

The Tuberculo-opsonic Index in Diagnosis and its Comparative Value with the Tuberculin Tests.

For the purpose of making a comparative study of the relative value of the tuberculo-opsonic index the von Pirquet tuberculin skin test, and the conjunctival tuberculin tests, these different tests were made upon about

200 cases of tuberculosis. The cases included all stages of bone and joint tuberculosis, advanced pulmonary tuberculosis, and the non-tuberculous inmates of a Home for Destitute Crippled Children. A series of two to four opsonic indices were obtained of each case, then the von Pirquet skin test applied, followed in about a week by the conjunctival tuberculin test. Wright's technic was used in estimating the opsonic index. A 25 per cent. solution of Koch's old tuberculin was used for the von Pirquet skin test, and a 1 per cent. solution of precipitated tuberculin in tablet form supplied by the experimental department of Parke, Davis and Co. was used in the conjunctival test.

The percentage results of the tests are given in Table 6.

1. The three tests do not agree in every case. Eighty per cent. of the cases that yielded positive results to both the von Pirquet and the conjunctival tests were verified by the opsonic index. The von Pirquet and conjunctival tests agreed in 92 per cent. of the non-tuberculous, in 69 per cent. of the cases of bone and joint tuberculosis, and in 64 per cent. of the cases of pulmonary tuberculosis.

2. In spite of the disparity in the results of the tests on the same cases, the sum total of positive results is very nearly the same for each of the tests.

3. As is to be expected theoretically, the more advanced the disease,—that is, the lower the reacting power of the individual,—the smaller the percentage of positive results to the tuberculin tests. There were only 45 per cent. positive von Pirquet reactions and 35 per cent. positive conjunctival reactions among the advanced cases of pulmonary tuberculosis, while there were 80 and 88 per cent. respectively positive among the cases of surgical tuberculosis.

4. A study of the tuberculo-opsonic indices shows that there is a larger percentage of fluctuating indices in the cases of advanced disease, and a larger percentage of low indices in the cases of less advanced disease. It is interesting to note that the percentage of variations of the opsonic index from the normal is about the same as the percentage of positive reactions to the tuberculin tests in the less advanced cases of tuberculosis, *e. g.*, being 77 per cent. as compared with 80 per cent. and 86 per cent. respectively, and is greater in the more advanced cases, *e. g.*, 65 per cent., as compared with 45 per cent. and 35 per cent. respectively.

5. There was some variation from the normal tuberculo-opsonic index of the indices of the non-tuberculous cases. This may, perhaps, be explained by the generally lowered resistance of many of these cases, even though they were clinically non-tuberculous. We have previously found that the normal tuberculo-opsonic index ranges from 0.8 to 1.2, as determined from an examination of over 100 healthy individuals.

TABLE 1.—SUMMARY OF DAILY RECORD OF TUBERCULO-OPSONIC INDICES DURING THE TREATMENT OF EIGHT CASES OF TUBERCULOSIS.

Patient No. 1.				Patient No. 2.				Patient No. 3.				Patient No. 4.			
T. O. I. before treatment.	No. of injection.	T. O. I. before injection.	Highest T. O. I. after injection.	T. O. I. before treatment.	No. of injection.	T. O. I. before injection.	Highest T. O. I. after injection.	T. O. I. before treatment.	No. of injection.	T. O. I before injection.	Highest T. O. I. after injection.	T. O. I. before treatment.	No. of injection.	T. O. I. before injection.	Highest T. O. I. after injection.
0.6	1	0.5	0.7	0.6	1	0.5	0.8	1.0	1	0.8	0.8	0.5	1	0.7	0.7
0.5	2	0.7	0.6	0.6	2	0.8	1.2	0.6	2	1.1	1.1	0.7	2	0.6	0.8
0.8	3	0.6	1.0	0.9	3	0.7	0.8	0.7	3	1.0	1.5	0.8	3	0.6	1.3
..	4	1.2	1.4	..	4	0.8	1.5	..	4	1.0	1.4	..	4	1.3	1.2
..	5	0.9	1.2	..	5	1.0	1.7	..	5	1.0	1.0	..	5	1.0	0.9
..	6	0.8	1.2	..	6	0.9	1.2	..	6	1.2	1.2	..	6	0.9	1.4
..	7	0.8	1.1	..	7	1.1	1.0	..	7	1.0	1.9	..	7	0.9	1.0
..	8	1.1	1.1	..	8	1.0	1.0	..	8	0.8	1.1	..	8	1.4	1.8
..	9	1.8	1.8	..	9	2.0	2.0	..	9	0.9	1.2	..	9	1.0	1.4
..	10	1.0	1.9	..	10	1.2	1.2	..	10	0.8	1.4	..	10	0.8	1.3
..	11	1.1	1.4	..	11	0.8	1.8	..	11	1.2	1.3	..	11	0.9	1.5
..	12	0.8	1.5	..	12	1.1	1.4	..	12	0.9	1.1	..	12	0.9	0.8
..	13	1.1	2.1	..	13	1.2	1.3	..	13	0.7	0.7	..	13	0.8	1.1
..	14	1.0	1.5	..	14	0.8	1.3	..	14	1.0	1.2	..	14	1.1	1.1
..	15	0.8	1.6	..	15	1.3	2.3	..	15	1.0	1.1	..	15	1.1	1.4
..	16	1.0	2.1	..	16	1.5	1.0	..	16	1.2	1.2	..	16	0 7	1.2
..	17	2.1	2.0	..	17	0.8	0.9	..	17	1.0	1.0	..	17	1.2	1.6
..	18	1.5	1.8	..	18	0.9	1.1	..	18	1.3	1.3	..	18	1.1	1.5
..	19	1.3	1.4	..	19	1.1	1.3	..	19	0.8	0.9	..	19	1.1	1.2
..	20	1.1	1.6	..	20	1.3	1.2	..	20	1.0	1.0	..	20	1.1	0.8
..	21	1.3	2.5	..	21	1.0	1.1	..	21	1.2	1.4	..	21	0.8	1.5
..	22	0.9	1.5	..	22	0.8	1.0	..	22	1.1	1.5	..	..	..	..
..	23	0.9	1.6	..	23	0.9	1.6	..	23	1.1	1.3	Patient No. 8.			
..	24	1.3	1.8	..	24	0.8	0.8	..	24	1.2	1.2	..	..	..	..
..	25	1.0	1.8	..	25	1.6	1.6	..	25	0.9	0.9	0.2	1	0.6	1.2
..	26	1.2	1.5	..	26	1.6	1.6	..	26	0.8	0.8	0.8	2	1.0	1.2
..	27	1.1	1.2	..	27	1.0	1.1	..	27	1.0	1.0	0.9	3	0.8	1.2
..	28	1.2	2.0	..	28	1.2	1.6	..	28	1.3	1.7	0.6	4	0.7	1.4
..	29	1.0	1.5	..	..	..	..	..	29	0.6	1.0	..	5	0.8	1.8

..	30	1.1	1.6		Patient No. 6.			..	..	..	..	..	6	1.4	1.4
..	31	0.9	1.3	..	..	..	..		Patient No. 7.			..	7	1.4	1.4
..	32	1.2	1.4	0.8	1	1.0	1.6	1.1	1	1.2	1.2	..	8	1.0	1.0
..	33	1.0	1.5	0.9	2	1.0	1.0	0.8	2	1.0	1.0	..	9	1.2	1.2
..	34	0.9	1.4	1.2	3	0.9	0.9	0.8	3	1.0	1.0	..	10	1.1	1.5
..	35	1.0	1.2	..	4	1.2	1.2	0.7	4	1.0	1.7	..	11	1.1	1.5
..	..	..	..	..	5	1.2	1.4	..	5	1.0	1.0	..	12	1.0	1.6
	Patient No. 5.			..	6	1.0	1.0	..	6	1.2	1.2	..	13	1.1	1.9
..	..	..	..	..	7	1.1	1.2	..	7	1.4	1.4	..	14	1.0	1.3
0.6	1	0.7	0.8	..	8	1.0	1.1	..	8	1.2	1.2	..	15	0.8	2.5
0.7	2	0.6	0.7	..	9	1.5	1.5	..	9	1.2	1.2	..	16	1.4	1.4
0.9	3	0.6	1.0	..	10	1.2	1.7	..	10	1.2	1.2	..	17	1.0	1.0
..	4	0.6	2.4	..	11	1.1	1.3	..	11	1.4	1.5	..	18	1.0	2.0
..	5	1.7	1.8	..	12	1.4	1.4	..	12	1.5	1.5	..	19	1.5	1.3
..	6	1.0	2.0	..	13	1.0	1.6	..	13	1.1	1.4	..	20	1.1	1.4
..	7	0.9	1.1	..	14	0.5	0.5	..	14	1.1	1.4	..	21	1.1	1.6
..	8	1.1	1.4	..	15	0.9	1.4	..	15	1.5	1.6	..	22	1.2	2.0
..	9	1.4	2.4	..	16	1.0	1.4	..	16	1.2	1.2	..	23	0.9	1.8
..	10	0.8	1.2	..	17	0.9	0.9	..	17	0.9	1.5	..	24	1.0	2.6
..	11	1.0	1.6	..	18	0.8	1.0	..	18	0.9	1.7	..	25	1.0	2.5
..	12	0.9	1.5	..	19	0.9	1.4	..	19	1.0	1.8	..	26	0.7	0.8
..	13	1.1	2.4	..	20	1.5	1.5	..	20	1.1	1.4	..	27	1.2	1.5
..	14	1.0	2.5	..	21	1.1	1.5	..	21	1.0	1.8	..	28	1.1	1.7
..	15	2.0	2.3	..	..	..	..	..	..	..	..	..	29	0.8	1.9
..	16	1.4	2.5	..	..	..	..	..	..	..	..	..	30	0.9	1.6
..	17	0.7	1.6	..	..	..	..	..	..	..	..	..	31	1.2	1.5
..	18	0.9	2.0	..	..	..	..	..	..	..	..	..	..	..	..
..	19	0.9	1.7	..	..	..	..	..	..	..	..	..	..	..	..
..	20	0.8	1.1	..	..	..	..	..	..	..	..	..	..	..	..
..	21	0.7	1.5	..	..	..	..	..	..	..	..	..	..	..	..
..	22	0.9	1.5	..	..	..	..	..	..	..	..	..	..	..	..
..	23	1.0	1.0	..	..	..	..	..	..	..	..	..	..	..	..
..	24	0.8	1.4	..	..	..	..	..	..	..	..	..	..	..	..
..	25	1.1	1.0	..	..	..	..	..	..	..	..	..	..	..	..
..	26	0.9	1.5	..	..	..	..	..	..	..	..	..	..	..	..
..	27	0.8	0.9	..	..	..	..	..	..	..	..	..	..	..	..

TABLE 2.—SAME SLIDES COUNTED BY DIFFERENT INDIVIDUALS.

Slide.	Counted by A.	Counted by B.	Slide.	Counted by A.	Counted by B.
1	0.9	1.2	24	0.8	1.4
2	1.1	1.3	25	0.9	0.7
3	0.4	0.6	26	0.9	0.9
4	0.9	1.1	27	1.4	1.0
5	1.0	1.0	28	1.1	1.0
6	0.4	0.3	29	0.9	1.1
7	0.9	1.1	30	0.8	1.4
8	0.9	1.8	31	1.1	1.1
9	0.9	1.0	32	0.6	0.8
10	1.1	1.1	33	0.9	0.6
11	1.0	1.2	34	1.3	1.1
12	0.8	1.0	35	1.0	1.0
13	0.7	0.9	36	0.9	0.9
14	0.9	1.2	37	0.9	0.7
15	0.9	0.9	38	0.8	1.0
16	0.8	0.3	39	1.2	0.7
17	0.6	0.7	40	1.1	1.1
18	1.2	1.1	41	0.9	1.0
19	0.9	0.8	42	0.4	0.8
20	0.9	1.1	43	1.0	0.9
21	1.1	1.2	44	1.0	1.0
22	0.6	0.7	45	0.8	1.1
23	0.6	0.7	46	0.9	0.9

TABLE 3.—THE OPSONIC INDEX OF SERUMS, USING DIFFERENT CREAMS.

Cream.	Opsonic Index. Serum 1.	Opsonic Index. Serum 2.	Opsonic Index. Serum 3.	Opsonic Index. Serum 4.	Opsonic Index. Serum 5.	Opsonic Index. Serum 6.	Opsonic Index. Serum 7.	Opsonic Index. Serum 8.	Opsonic Index. Serum 9.	Opsonic Index. Serum 10.
A	1.5	1.6	1.7	1.3	1.0	1.0	0.6	0.8	0.4	1.5
B	1.4	1.5	1.5	0.7	0.8	0.5	0.7	0.9	1.0	1.2
C	2.0	1.5	2.2	0.7	0.8	1.1	0.9	1.0	0.8	1.2
D	1.4	1.4	1.4	1.0	0.5	1.0	0.9	0.6	0.7	0.9
E	1.5	1.4	1.5	0.8	1.0	0.7	1.0	0.8	1.0	1.9

TABLE 4.—THE OPSONIC INDEX OF SERUMS, USING BACTERIAL EMULSIONS OF ONE-HALF, ONE-FOURTH, ONE-SIXTH, AND ONE-EIGHTH DILUTIONS.

Emulsion.	Opsonic Index. Serum 1.	Opsonic Index. Serum 2	Opsonic Index. Serum 3.	Opsonic Index. Serum 4.	Opsonic Index. Serum 5.	Opsonic Index. Serum 6.	Opsonic Index. Serum 7.
Diluted one-half	0.9	0.9	2.7	1.3	0.4	0.9	0.5
" one-fourth	1.1	0.9	2.1	1.7	1.2	1.3	0.4
" one-sixth	1.2	1.2	1.6	1.0	0.8	1.4	0.9
" one-eighth	1.3	1.3	..	..	..	..	..

TABLE 5.—RATIO BETWEEN THE OPSONIC INDEX OF FULL-STRENGTH SERUM AND DILUTED SERUM.

Test I. Serum Diluted Two Times; Hence Compare Following Ratios with 2.				Test II. Serum Diluted Four Times; Hence Compare Following Ratios with 4.				Test III. Serum Diluted Ten Times; Hence Compare Following Ratios with 10.			
Serum A.	Serum B.	Serum C.	Serum D.	Serum A	Serum B.	Serum C.	Serum D.	Serum A.	Serum B.	Serum C.	Serum D.
2.0	1.6	0.9	1.6	0.9	1.0	1.4	2.0	2.0	1.7	1.0	2.1
1.3	1.2	0.9	1.3	1.7	1.4	1.0	2.0	2.0	2.7	1.7	2.6
1.8	1.1	1.6	1.1	1.4	0.9	1.6	1.8	3.0	1.8	1.9	5.5
1.6	1.0	1.4	0.9	1.8	0.9	2.3	1.7	1.8	1.0	2.0	2.5
2.1	1.1	1.0	2.3	2.4	1.9	2.1	2.0	2.4	1.4	3.0	3.2
1.7	1.7	3.0	1.2	1.7	1.5	2.5	1.4	2.5	1.3	2.5	2.2
Average = 1.2.				Average = 1.6.				Average = 2.2.			

TABLE 6.—PERCENTAGE OF POSITIVE REACTIONS TO THE VON PIRQUET TUBERCULIN SKIN TEST, THE CONJUNCTIVAL TUBERCULIN TEST, AND THE TUBERCULO-OPSONIC INDEX.

Classes of Cases.	Number of Cases.	Von Pirquet Tuberculin Skin Test.	Conjunctival Tuberculin Test.	One or More Opsonic Index Out of the Normal Range, *e.g.*, 0.8 to 1.2.	Two or More Opsonic Indices Out of the Normal Range.	Average of the Opsonic Indices Out of the Normal Range.
		Per Cent. Positive.	Per Cent. Positive.	Per Cent. Positive.	Per Cent. Positive.	Per Cent. Positive.[1]
Non-tuberculous	31	1	0	35	2	1
Bone and joint tuberculosis	75	80	86	75	43	37
Advanced pulmonary tuberculosis	117	46	35	74	26	31

L'Index opsonique tuberculeux dans le Diagnostic et dans le Traitement de la Tuberculose.—(Lincoln.)

I. Rapport sur l'emploi de l'index opsonique tuberculeux comme guide thérapeutique dans le traitement par la tuberculine de la tuberculose, pendant une période d'environ deux ans.

II. L'index opsonique tuberculeux dans le diagnostic de la tuberculose. Valeur comparée de l'index opsonique tuberculeux, l'épreuve de von Pirquet sur la peau avec la tuberculine, et l'épreuve à la tuberculine sur la

conjonctive, dans le diagnostic de la tuberculose, avec rapport sur les essais faits sur 200 cas.

III. Exactitude de l'index opsonique tuberculeux prouvée par—

(*a*) La dilution des opsonins.

(*b*) La vie des opsonins.

(*c*) Le chauffement des opsonins.

Der tuberkulöse opsonische Index in der Diagnose und Behandlung der Tuberkulose.—(LINCOLN.)

I. Bericht über den Gebrauch des tuberkulösen opsonischen Index als einen therapeutischen Führer in der Tuberkulinbehandlung der Tuberkulose während eines Zeitraums von zwei Jahren.

II. Der tuberkulöse opsonische Index in der Diagnose der Tuberkulose.

Vergleichender Wert des tuberkulösen opsonischen Index, der von Pirquet'schen Tuberkulin-Hautprobe und der Bindehaut-Tuberkulinprobe in der Diagnose von Tuberkulose mit einem Bericht der Proben an 200 Fällen.

III. Genauigkeit des tuberkulösen opsonischen Index, probiert durch—

(*a*) Verdünnung des Opsonins.

(*b*) Leben des Opsonins.

(*c*) Erwärmen des Opsonins.

UEBER OPSONINE UND DEREN VERWENDBARKEIT IN DER DIAGNOSE, PROGNOSE UND THERAPIE DER TUBERKULOSE.

Von Dr. Johann v. Szabóky,
Budapest-Gleichenberg.
(Kurze, zusammenfassende Mitteilung.)

Nach an mehr wie 100 Personen ausgeführten Untersuchungen schloss ich Folgendes:

1. Der Wert des Opsoninindexes gesunder Personen schwankt zwischen 0.85 und 1.15. An einer und derselben Person vorgenommene Untersuchungen ergaben keinen ständigen, sondern nur einen innerhalb der normalen Grenzen schwankenden Wert.

2. Wenn der Wert des Opsoninindexes unter 0.85 und über 1.15 war, konstatierte ich meistens Tuberkulose. Die Untersuchung hat sich bei 85 von 99 Tuberkulosefällen, bei 5 von 8 chirurgischen und bei allen Lupus vulgaris-Fällen bewährt.

3. Meine parallel mit den probatorischen Tuberkulininjektionen vorgenommenen Opsoninindex-Untersuchungen zeigten, dass das Sinken des Opsoninindexes—selbst wenn dasselbe der klinischen Reaktion auch weit vorangieng,—das Vorhandensein von Tuberkulose bewies. Auf Grundlage meiner Untersuchungen kann auch angenommen werden, dass das Sinken des Opsoninindexes, sei es nach einer kleinen oder grossen Dosis, ebenfalls Tuberkulose bedeutet.

4. Aus der Höhe des Wertes des Opsoninindexes können wir auf den Grad des Leidens keine Folgerungen ziehen, es ist aber wahrscheinlich, wie dies etwa 14 Untersuchungen zeigen, dass das starke Sinken des Opsoninindexes eine schlechte Prognose bedeutet.

5. Opsoninuntersuchungen an 17 Kranken ergaben, dass in der spezifischen Therapie die Bestimmung des Opsoninindexes einen Fortschritt bildet, weil wir durch diese Krontrolle die Reaktion häufig vermeiden können und in der Lage sind, den Grad der Immunisation approximativ feststellen zu können. Wenn auch die während der Immunisation auftretende Opsoninindexsteigerung nicht in allen meiner Fälle die klinische Besserung im Gefolge hatte (dies zeigt schön die VII.: trotzdem das Leiden vorgeschritten ist, stieg der Opsoninindex fortwährend), habe ich bei Fällen beginnender. Lungentuberkulose oft ziemlich gute Resultate erzielt. Die Feststellung des Wertes des Opsoninindexes kann als guter Anhaltspunkt insbesondere

in vorgeschrittenen fieberhaften Fällen dafür dienen, ob die begonnene Behandlung ohne Schädigung des Organismus fortgesetztwerden kann, oder nicht; im Allgemeinen sehen wir erst bei diesem Kontrollverfahren, wie schwer die spezifische Behandlung ist, wie schwer es ist, die gehörige Dosis zu wählen, welche Praxis zur richtigen Individualisierung gehört, wie unrichtig die häufige Einspritzung und die rasche Steigerung der Dosis ist.

6. Die Tierversuche bieten keinen genügenden Anhaltspunkt dafür, dass auf Grund der mit Human- und Bovinemulsion vorgenommenen Opsoninuntersuchungen die doppelte oder die reine Human- oder die reine Bovininfektion ungenommen werden konnte.

Nach alledem glaube ich, dass die Feststellung des Opsoninindexes bei der Diagnose der Tuberkulose (Bradschaw und Blynn) eine ziemlich wichtige Rolle spielt. Es erleichtert in vielen Fällen, wie ich glaube, schon jenen Umstand, dass wir nach der Diagnose der Tuberkulose am folgenden Tage eine halbe resp. Stunde (Faser) das Sinken des Wertes des Opsoninindexes erzielen. Wenn wir hiebei jene Vorteile in Betracht ziehen, welche die Feststellung des Opsoninindexes in der Therapie der Tuberkulose und eventuell in der Prognose der Tuberkulose (French, Clive Riviere, Rotch, Floyet, Neuburger, Bunch, Balban, Cecil Rosanquet, Bradschaw und Glynn) bieten kann, dann dürfen wir nicht vor den technischen Schwierigkeiten zurückschrecken. Ich muss nun allerdings zugeben, dass die Opsoninbestimmung eine sehr mühsame, zeitraubende Untersuchung ist, welche eine kolossale übung beansprucht. Nur nach einer längeren Einreibung ist es möglich, gleichmässige Resultate zu erzielen und dann spricht aber noch immer die Subjektivität einzelner Untersucher eine ziemlich wichtige Rolle.

DISCUSSION.

Dr. J. Denys (Louvain): Malgré les problèmes interessants soulevés par les travaux de Wright et d'autres sur l'index opsonique dans la tuberculose, je ne pense pas que cet index soit de grande valeur, et cela pour la raison qu'il y a de trop grandes différences entre la façon dont nous nous défendons contre l'infection tuberculeuse et la façon dont nous nous defendons contre la plupart des autres infections.

Dans l'infection streptococcique par exemple, le rôle décisif revient aux leucocytes. Dès que ceux-ci parviennent à phagocyter les streptocoques, l'infection est vaincue. C'est avec mon élève le Dr. Leclef, qu'en 1896, c'est à dire, longtemps avant Wright, que j'ai prouvé que cette phagocytose était provoquée par la présence dans le sérum d'une substance spéciale, qui se combine avec les streptocoques, et les rend phagocytables. A cette substance, Wright a donné le nom d'opsonine. La résistance qu'un animal offre à l'infection streptococcique est proportionnelle à sa richesse en opsonine.

Il en est de même dans les infections par le pneumocoque, le coli-bacille, le bacille de la peste. Dans l'infection tuberculeuse, la lutte décisive se passe non pas entre les leucocytes et des bacilles, mais entre ceux-ci et les cellules fixes; principalement les cellules du tissu conjonctif et les cellules endothéliales. Les leucocytes des animaux très sensibles à la tuberculose phagocytent très energiquement les bacilles, comme on peut s'en assurer en injectant dans le peritoine des cobayes. 24 heures après ces leucocytes chargés de bacilles sont phagocytés par les cellules endothéliales et y sont dégénérés. Les bacilles restent inaltérés et se trouvent dès lors directement dans les cellules endothéliales, où la lutte commençera réellement.

Autre fait: les leucocytes des urines des malades atteints de cystite tuberculeuse phagocytent très énergiquement les bacilles de la tuberculose ajoutés en émulsion. Malgré ce grand pouvoir de phagocytose, ce malades succombent s'ils sont abandonnés à leurs propres ressources. Ces deux faits, pris entre d'autres, nous montrent que la phagocytose ne joue pas dans la tuberculose le rôle décisif qu'elle a dans d'autres infections. La détermination de l'index opsonique ne peut donc avoir qu'une valeur très secondaire pour juger la résistance des malades pour conclure à bonne fin, une cure spécifique, la fixation de l'index opsonique n'est pas nécessaire.

Dr. L. Detre (Budapest): D'abord qu'il me soit permis de saluer ici Dr. Denys, qui longtemps avant Dr. Wright a découvert ce que nous appelons maintenant "force opsonique" du sérum. Mais quant au rôle des leucocytes, nous ne sommes pas d'accord. Ce ne sont pas des cellules fixes, mais bien des leucocytes, spécialement les cellules mononucléaires, qui dévorent les phagocytes pleins de bacilles tuberculeux; au centre des mononucléaires on peut alors trouver des bacilles plus ou moins digérés. Les leucocytes du tuberculeux quelquefois n'attaquent pas les bacilles de l'individu, mais alors il s'agit ici d'une immunité des bacilles envers les leucocytes; si nous renforçons par des inoculations de tuberculine la force de ces cellules, nous changeons—en sens favorable—la résistance de l'organisme en augmentant la force phagocytaire. En présence de la relation étroite entre l'opsonic index et la résistance cellulaire, nous pouvons admettre que les investigations opsoniques sont réellement utiles au cours du traitement spécifique de la tuberculose. Bien entendu, moi, je m'en passe, parceque dans mon dispensaire spécifique à la Charité-Policlinique à Budapest, j'ai trouvé une autre méthode qui nous permet d'établir d'une façon plus facile et plus objective, l'état actuel de sensibilité de l'organisme. J'en parlerai plus tard lors de ma communication sur la méthode différentielle cutanée.

At the end of this discussion Dr. Vincent Y. Bowditch, President of Section II, took the chair.

SUR L'EMPLOI DES RÉACTIONS CUTANÉES ET CONJONCTIVALES A LA TUBERCULINE (CUTI ET OPHTALMO-RÉACTIONS) DANS LE DIAGNOSTIC DES INFECTIONS TUBERCULEUSES.

Par le Prof. A. Calmette,

Lille.

Bien que les méthodes de diagnostic précoce de la Tuberculose que von Pirquet, Wolff-Eissner et moi avons fait connaître, soient employées par les cliniciens seulement depuis un peu plus d'une année, elles ont donné lieu à un nombre considérable de travaux, presque tous nettement confirmatifs des faits que nous avions signalés.

L'utilité et l'importance de ces méthodes n'ont plus besoin d'être démontrées. L'empressement avec lequel elles ont été accueillies par le public médical indique assez qu'elles réalisent un progrès sensible sur les procédés diagnostiques dont nous disposions précédemment. L'enthousiasme de beaucoup de médecins a même été tel qu'il a fallu réagir contre certaines exagérations de leur emploi, exagérations qui n'étaient pas sans présenter quelques dangers.

Les réactions cutanées et conjonctivales à la tuberculine devant faire l'objet de plusieurs communications au Congrès international de Washington, je crois utile de préciser dans cette courte note les conclusions qui se dégagent de mon expérience personnelle à leur sujet.

Avec la collaboration de mes élèves Maurice Breton, Minet, Léon Petit et de nombreux médecins qui ont bien voulu m'envoyer les résultats de leurs essais, j'ai pu réunir jusqu'à présent 6.303 observations cliniques relatives à l'ophtalmo-réaction seule.

Ces 6.303 observations peuvent être résumées comme suit:

2.894 sujets cliniquement tuberculeux ont fourni 2.664 ophtalmo-réactions positives, soit 92.05 % et 230 réactions négatives, soit 7.95 pour cent.

1.081 sujets cliniquement suspects de tuberculose ont fourni 616 ophtalmo-réactions positives, soit 57 pour cent et 464 réactions négatives, soit 43 pour cent.

2.328 sujets sains ou cliniquement indemnes, tant à l'hôpital qu'en dehors du milieu hospitalier, ont fourni 391 opthalmo-réactions positives, soit 16.8 pour cent et 1.937 réactions négatives, soit 83.2 pour cent.

D'autre part sur 55 protocoles d'autopsies faites sur des sujets, enfants ou adultes, qui avaient fourni une réaction conjonctivale positive alors que l'on n'avait pas soupçonné chez eux l'existence de la tuberculose, on a trouvé 49 fois des lésions tuberculeuses macroscopiquement visibles, localisées pour le plus grand nombre dans les ganglions trachéo-bronchiques et pour quelques-uns dans d'anciens foyers ayant déterminé des adhérences pleurales.

L'innocuité de la méthode lorsqu'on emploie une tuberculine convenablement préparée et aseptique apparaît certaine, car sur nos 6.303 épreuves, les seules complications relevées ont été 3 kératites phlycténulaires, 20 conjonctivites et 72 réactions prolongées pendant plus de trois semaines. On n'a jamais observé d'accidents plus graves, et dans aucun cas il n'est résulté de troubles fonctionnels de la vue ni de lésions oculaires persistantes.

D'une manière générale on peut affirmer que les réactions hâtives moyennes et fortes s'observent le plus souvent chez les sujets porteurs de lésions bénignes insoupçonnées et chez les suspects, tandis que les tuberculeux avérés réagissent presque toujours tardivement et avec peu d'intensité. Il semble donc que, comme l'a déjà indiqué Wolff-Eissner, l'allure des réactions fournit un élément précieux pour le pronostic.

Les malades cachectiques, et aussi ceux qui sont atteints de granulie aigüe, de péritonite ou d'infections tuberculeuses hypertoxiques, ne réagissent que très faiblement, tardivement (après 48 heures) ou pas du tout. Les sujets dont il s'agit ne réagissent alors ni à la réaction cutanée de von Pirquet, ni à l'injection sous-cutanée de tuberculine.

L'expérimentation sur les animaux, aussi bien que les observations cliniques sur l'homme attestent que l'ophtalmo-diagnostic révèle presque toujours l'existence de foyers tuberculeux en activité ou en évolution. Les simples "porteurs de bacilles" sans lésions tuberculeuses et les sujets porteurs de lesions calcifiées ou guéries ne réagissent pas.

La spécificité de l'ophtalmo-diagnostic est égale à celle de l'injection sous-cutanée de tuberculine.

Le nombre relativement considérable des sujets en apparence sains qui fournissent une réaction positive (16.8 pour cent) atteste en même temps la grande valeur du procédé comme moyen de diagnostic précoce, la fréquence des tuberculoses latentes et la merveilleuse curabilité spontanée de ces dernières.

La répétition des instillations de tuberculine chez les sujets sains ne fournit jamais de réaction si l'on prend soin de renouveler chaque instillation moins de cinq jours après la précédente. Si l'on attend plus de cinq jours, il peut se produire une anaphylaxie locale de la muqueuse oculaire qui est

alors susceptible de fausser le diagnostic. Cette anaphylaxie locale disparaît au bout de 25 jours environ.

Les sujets tuberculeux récemment traités par des injections sous-cutanées de tuberculine ne fournissent en général aucune réaction oculaire, sauf lorsque le traitement a été suspendu depuis plus d'un mois.

Lorsqu'on injecte de la tuberculine sous la peau de sujets antérieurement soumis à l'ophtalmo-réaction, la rougeur conjonctivale peut réapparaître même après six semaines, rarement plus tard, sans qu'on instille de nouvelle tuberculine dans l'œil. Cette réapparition de la rougeur conjonctivale, s'observe même lorsqu'on injecte la tuberculine dans le rectum.

En étudiant comparativement les effets de la cuti-réaction de von Pirquet et ceux de l'ophtalmo-réaction, j'ai pu me convaincre que, chez les enfants âgés de moins d'un an, la cuti-réaction doit être préférée, car elle fournit alors des indications tout aussi fidèles que l'instillation conjonctivale, et elle est d'un emploi plus commode en même temps que plus surement inoffensif. On trouve alors que dans les hôpitaux, 20 pour cent environ des enfants réagissent au cours de la première année.

Au-delà de l'âge d'un an le nombre des sujets sensibles à la cuti-réaction devient énorme. Il atteint 60 pour cent à l'âge de 15 ans et, chez les adultes, le nombre des sujets qui réagissent, quoique tout-à-fait sains en apparence, est tellement considérable qu'il est impossible de tirer de cette réaction, lorsqu'elle est positive, des indications utiles, surtout au point de vue du diagnostic précoce. Il semble que la cuti-réaction reste positive chez tous les sujets qui sont ou ont été porteurs de lésions tuberculeuses, alors même que celles-ci sont enkystées depuis longtemps.

Au contraire, chez les enfants âgés de plus d'un an, et chez les adultes, l'ophtalmo-diagnostic, ne révélant que des tuberculoses actives, donne des résultats beaucoup plus précis. On doit donc lui donner la préférence, malgré l'inconvénient qu'il présente de permettre au malade de lire sur son œil le diagnostic de l'affection dont il est atteint. Cet inconvénient est d'ailleurs de minime importance car il est toujours facile au médecin de tromper son malade s'il le juge utile, ou de lui expliquer l'intérêt capital que présente pour sa guérison l'établissement d'un diagnostic précoce.

Dans les milieux hospitaliers, j'estime qu'il est recommandable de recourir simultanément aux deux méthodes qui se contrôlent alors l'une par l'autre.

Sur 53 malades cliniquement tuberculeux réagissant positivement à l'ophtalmo-diagnostic, j'ai pu constater ainsi que 48 fournissaient une réaction également positive à l'épreuve cutanée de von Pirquet et que, par contre, sur 43 non cliniquement tuberculeux, 22 réagissaient à la cuti-réaction, tandis que 17 seulement de ces derniers donnaient en même temps une réaction positive à la réaction conjonctivale.

Il est donc évident que la constatation d'un résultat positif par la double épreuve faite le même jour chez un sujet suspect, doit permettre au clinicien d'affirmer presque sûrement l'existence d'un foyer tuberculeux en activité.

On ne doit pas exagérer l'importance de ces nouvelles méthodes de diagnostic basées sur les réactions locales à la tuberculine: elles ne devront jamais faire négliger les autres moyens d'information que nous offrent la clinique et le laboratoire, mais il paraît incontestable que, judicieusement employées, elles rendront les plus grands services, et qu'elles nous apporteront une aide précieuse dans la lutte sociale contre la tuberculose.

Je crois utile de terminer cette note par quelques considérations sur le mécanisme des réactions tuberculiniques locales ou générales. Il me paraît que ces réactions sont dues à la fixation de la tuberculine par les organes ou les cellules riches en lécithine, et à la combination qui en résulte entre la tuberculine et la lécithine de ces cellules ou de ces organes.

Lorsqu'un animal sain est entoxiqué par de fortes doses de tuberculine, il est remarquable de constater que des capsules surrénales sont toujours fortement congestionnées. Or on sait que, comme l'a demontré Léon Bernard, ces glandes á sécrétion interne sont particulièrement riches en lécithine.

D'autre fait, j'ai constaté que le sérum des animaux tuberculeux (homme, bœuf, porc) renferme presque toujours de la lécithine libre, capable d'activer le venin de cobra, c'est à dire de le rendre hémolytique, tandis que le sérum de ces mêmes animaux sains n'en renferme pas.

J'ai constaté en outre que la tuberculine et les bacilles tuberculeux sont capable de fixer in vitro la lécithine, et cette réaction est mise en évidence par l'activation de venin laquelle est toujours immediate lorsque venin et globules rouges lavés sont mis en contact, tandis qu'elle ne se produit plus lorsque la lécithine a eté mise en contact avec la tuberculine ou les bacilles d'abord, pendant deux heures, puis avec le venin et les globules lavés.

Il semble donc qu'une relation étraite existe d'une part entre la présence de lécithine libre dans le sang de l'homme, du bœuf et du porc, et l'infection tuberculeuse; d'autre part entre la lécithine libre, capable de fixer la tuberculine et les réactions tuberculiniques générales ou locales.

Die Anwendung der Haut- und Conjunktivreaktionen in der Diagnose der Tuberkelinfektionen.—(CALMETTE.)

Unter 2894 Klinischtuberkulösen, gab 92.05% Conjunktivreaktionen; unter 1081 in klinischen Verdachtstehenden, reagirten 57%; und unter 2328 entweder scheinbar gesunden oder nicht in Verdachtstehenden, reagirten 16.8%.

Bei 55 Kindern oder Erwachsenen, die vorher conjunktiv reagirt hatten,

obgleich sie nicht im Verdacht der Tuberkulose standen und die zur Obduction kamen, wurden mikroskopische Verletzungen, am häufigsten in den Bronchialdrüsen entdeckt.

Unter 6303 Reaktionen, merkte man nur Komplicationen: in 3, phlyctenular Keratitis; in 20, Conjunctivitis; und in 72, über drei Wochen ausgedehnten Reaktionen.

Schwerere Störungen noch dauerende Augenverletzungen oder Gesichtsfehler sind in keinen Falle vorgekommen.

Im allgemeinen wurden die früheren Reaktionen am häufigsten bei den Tuberkulösverdächtigen und die späteren und kleineren Reaktionen bei den wirklich Tuberkulösen bemerkt.

Miliartuberkulösen, die an Bauchfellentzündung leidenden Tuberkulösen und hypertoxikologische Tuberkelinfektionen reagiren schwach, spät oder gar nicht auf die conjunktival, so wohl als auf Haut- und Unterhautreaktionen.

Klinische und experimentelle Beobachtungen beweisen, dass die Augenprobe beinahe immer active oder entwickelende Tuberkelherde offenbart, nicht bei einfachen Bazillen trägern und denjenigen mit verkalten oder geheilten Lesionen, negativ ausfällt obwohl die letzteren, wie es scheint, oft auf die Hautprobe reagiren.

Wiederholte Tuberkulineinspritzungen bei Gesunden sind nie positive wenn die Zwischenzeit zwischen, nacheinanderfolgenden Einspritzungen nicht fünf Tage übertrifft, Oertliche Anaphylaxe verschwindet in ungefähr 25 Tagen.

Im allgemeinen kommt keine augenscheinliche Reaktion bei den mit subkutanen Einspritzungen von Tuberkulin behandelten Kranken bis wenigstens ein Monat nach vollendeter Behandlung.

So spät als sechs Wochen nach der Augenprobe erscheint manchmal die Conjunctivröthe als Resultat der Unterhauttuberkulineinspritzung wieder.

Für Kinder unter einem Jahre zieht man die Hautprobe, welche augenblicklich 20% Reaktionen in Spitälern giebt, vor, da man sie für die bequemste and harmloseste hält. Ueber dieses Alter hinaus, vergrössert sich die Zahl der Hautprobeempfindlichen bis sie beim 15ten Jahre 60% erreicht, und bei Erwachsenen wird die Zahl der Reaktionen so Kolossal, dass man keine nützliche Indikationen für eine Frühdiagnose erhält. Trotz ihrer Unbequemlichkeit zieht man daher die Conjunktivalprobe für Erwachsene vor. In Spitälern ist der gleichzeitige Gebrauch beider Proben zu empfehlen.

Eine Reaktion auf beide Proben giebt uns einen überzeugenden Beweis von der Existenz eines activen Tuberkelherdes. Eine wichtige Stelle behalten jedoch immer noch ander wohlanerkannte diagnostische Verfahren, sowohl klinische wie Laboratoriumsverfahren.

The Application of the Cutaneous and Conjunctival Tuberculin Reactions in the Diagnosis of Tuberculous Infections.—(CALMETTE.)

Of 2894 clinically tuberculous patients, 92.05 per cent. gave positive reactions to the conjunctival test; of 1081 persons with clinical suspicion of tuberculosis, 57 per cent. were positive, and of 2328 persons either apparently healthy or without suspicion of tuberculosis, 16.8 per cent. were positive with the same test.

Of 55 children or adults who had given positive conjunctival reactions, not previously suspected of tuberculosis, and who came to postmortem, macroscopic lesions were detected in 49.

In 6303 tests, the only complications noted were in 3 phlyctenular keratitis, in 20 conjunctivitis, and in 72 reactions prolonged beyond three weeks. In no instance did graver disturbances or permanent ocular lesions or visual defect occur.

In general, early reactions are observed most frequently with suspected tuberculosis, and late and slight reactions with developed tuberculosis. Cachectic patients and those with acute miliary tuberculosis, tuberculous peritonitis, and hypertoxic tuberculous infections react very feebly, late, or not at all with the conjunctival as well as with the cutaneous and subcutaneous tests.

Experimental and clinical observations demonstrate that the ophthalmic test reveals almost always active or developing tuberculous foci, but is negative with simple carriers of bacilli and with those with calcified or healed lesions, who, it would seem, often react to the cutaneous test.

Repeated instillations of tuberculin in healthy subjects never give a reaction when the interval between successive instillations does not exceed five days. Local anaphylaxis disappears in about twenty-five days.

In general no ocular reaction occurs in patients treated with subcutaneous injections of tuberculin until over a month after suspension of treatment.

Conjunctival redness may reappear as the result of subcutaneous injection of tuberculin as late as six weeks after submission to the ophthalmic test.

For children under one year the cutaneous test which at this period gives 20 per cent. of positive results in hospitals, is to be preferred as the more convenient and inoffensive procedure. Beyond this age the number of persons susceptible to the cutaneous test increases, and at fifteen years becomes 60 per cent., and with adults the number giving positive reactions is so enormous that no useful indications for early diagnosis can be drawn. Hence, in spite of its inconvenience, the conjunctival test is to be preferred for children over one year, and for adults. In hospitals the simultaneous employment of both tests is to be recommended.

A positive result by the double test furnishes almost conclusive evidence of the existence of an active tuberculous focus.

ERFAHRUNGEN ÜBER DIE KUTANE TUBERKULIN-REAKTION AN 200 OBDUZIERTEN KINDERN.

Von Privatdozent Dr. C. von Pirquet,
Aus der K. K. Universitäts-Kinderklinik Wien
(Vorstand Hofrat Escherich).

Im vorigen Herbste habe ich (Festschrift der Tuberkulose-Konferenz, Wien, 1907, und Wiener klinische Wochenschrift, 1907, 38) über die ersten 100 Sektionen berichtet, welche Kinder betrafen, die der kutanen Tuberkulinprobe unterzogen worden waren. Jetzt ist das zweite Hundert von Obduktionen erreicht. Ich werde neben den neuen Fällen auch die schon besprochenen soweit heranziehen, als sich für ihre Beurteilung neue Gesichtspunkte ergeben haben.

Angewendete Methoden: Die ersten 100 Fälle waren fast durchwegs in der Weise geimpft worden, dass ich neben einer Kontrollstelle zwei Impfstellen mit 25% Tuberkulin anlegte. In der jetzigen Beobachtungsreihe sind fast überall Impfungen mit unverdünntem Alttuberkulin vorgenommen worden. In einem Teile der Fälle wurden daneben quantitative Abstufungen des Tuberkulins in der Progression 10, 100, 1000 oder 4, 16, 64 durchgeführt. Die Impfung erfolgte stets mit meinem Impfbohrer, meistens am rechten Unterarm, manchmal an anderen Körperstellen.

In einer Anzahl von Fällen wurde die konjunktivale und dermale Probe ausgeführt. Von der konjunktivalen Applikation (Wolff-Eisner, Calmette) beim Menschen bin ich wieder ganz abgekommen, da sie in einzelnen Fällen sehr heftige, unangenehme und langdauernde Reizerscheinungen der Konjunktiva verursacht und es ausserdem wegen des Widerstandes der Kinder schwer ist, die Einträufluug in gleichmässiger Weise durchzuführen. Die konjunktivale Reaktion ist bei einer 1% Verdünnung von Alttuberkulin viel unempfindlicher als die kutane, beschränkt sich aber nicht, wie mehrfach behauptet wurde, auf aktive Herde. Die Unterschiede zwischen beiden Reaktionen sind nur quantitativer Natur. Wenn man höhere Konzentrationen Tuberkulin im Auge anwendet, so wie ich es mit Schnürer bei Kühen getan habe, so gleicht sich der Unterschied in der Häufigkeit vollkommen aus. Die Anwendung entsprechend starker Lösungen im Auge ist aber beim Menschen nicht zu erlauben. Eine Unterscheidung zwischen aktiven und inaktiven Herden ist, so sehr sie wünschenswert wäre, mit den neueren

Applikationsarten ebenso wenig erreicht, als mit der Koch'schen Injektion. Frische Tuberkulosen sind wohl im Allgemeinen empfindlicher, eine prinzipielle Abgrenzung ist aber noch nicht festgestellt.

Die in meiner ersten Publikation ausgesprochenen Hoffnungen, dass die Verwertung der Eintrittszeit, der Grösse, oder der Verdünnung des Tuberkulins, bei der die Reaktion eintritt, uns einen genaueren Hinweis auf den tuberkulösen Prozess geben wird, hat bis jetzt noch kein vollkommenes Resultat geliefert. Zu verwerten sind in dieser Hinsicht nur, wie ich später ausführlicher bringen werde, die torpide und die kachektische Reaktion. Im Uebrigen ist bisher nur der Schluss sicher, dass jeder positiven Reaktion eine tuberkulöse Infektion zu Grunde liegt. Ob eine klinische Einzelerscheinung gerade tuberkulöser Natur ist, kann aus dem positiven Ausfall nicht unmittelbar geschlossen werden.

Die dermale Reaktion, die entzündliche Wirkung des Tuberkulins ohne nachweisliche äussere Verletzung der Haut, welche von Moro durch Einreibung der Haut mit Tuberkulin-Lanolin, in Frankreich von Lignières und Berger durch Einreibung von Tuberkulin allein erzielt wird, hatte ich zuerst nur in einem Falle von hochgradiger Ueberempfindlichkeit gesehen. Bei genauer Befolgung der Vorschriften von Moro in Bezug auf die Verfertigung der Salbe und insbesondere auf die 100 malige Reibung erzielte aber R. Monti an unserer Klinik fast in allen Fällen positiver Kutanreaktion auch die Entstehung einer dermalen Reaktion. Für jenen Arzt, welcher die Impfung scheut, ist die Einreibung ein gutes diagnostisches Mittel und sie ist sicher der konjunktivalen Reaktion wegen ihrer völligen Unschädlichkeit bei Weitem vorzuziehen. Die kutane Wirkung hat jedoch vor ihr den Vorteil der grösseren Exaktheit, des schärferen millimetrisch messbaren Impfeffektes und der schnelleren Ausführung. Insbesondere für klinische, quantitative und für täglich fortgesetzte Untersuchungen ist darum die kutane Reaktion der dermalen Modifikation überlegen. Gerade in der vorliegenden Untersuchungsreihe habe ich in vielen Fällen die Proben und quantitativen Messungen wochenlang täglich ausgeführt, um dadurch zusammenhängende Bilder über die Reaktionsfähigkeit bei Meningitis tuberculosa und bei Masern zu gewinnen. Zu solchen Versuchsreihen ist nur die Kutanreaktion geeignet.

Endlich wurden bei einer grösseren Zahl von Kindern der zweiten Serie durch F. Hamburger Injektionen von Tuberkulin vorgenommen. Seine Beobachtungen waren hauptsächlich auf die Stichreaktion gerichtet und er konnte nachweisen, dass dieselbe in einem Teile der Fälle negativer Kutanreaktion positiv ausfiel, dass sie daher als die empfindlichere anzusehen ist. Diese Art von Fällen betrifft fast ausschliesslich ältere Kinder mit nicht manifester Tuberkulose, welche viel seltener im Spitale sterben, als kleine Kinder mit manifester Tuberkulose. Sie sind daher in den Sek-

tionsfällen in einem viel geringeren Prozentsatze zu finden, als bei der Statistik der intravitalen Untersuchungen.

In dieser Beobachtungsreihe wurden überhaupt viel häufiger mehrfache Untersuchungen vorgenommen, als in der ersten Serie. Dort waren nur 20 Kinder mehrmals, die übrigen nur einmal geimpft worden; hier wurden mehrmalige Proben in 58 Fällen mit 350 Einzeluntersuchungen ausgeführt. Die Revision geschah alle 24 Stunden durch 3–8 Tage. Notiert wurde jedesmal der Querdurchmesser der Efflorescenz in Millimetern, der Grad ihrer Tastbarkeit (deutlich, undeutlich, nicht tastbar) endlich Farbe und sonstige Besonderheiten von der Norm abweichender Reaktionen.

Die Sektionen wurden fast ausnahmslos durch Herrn Professor Ghon in ausserordentlich exakter Weise durchgeführt, welcher in einigen Fällen an die makroskopische Leichenschau auch mikroskopische Untersuchungen anschloss. Tierversuche durch Injektion von Drüsenmaterial in Meerschweinchen wurden nicht gemacht.

Alle 200 Obduktionen lassen sich nach dem Resultate der intravitalen Reaktion und der postmortalen Untersuchung in folgender Weise gruppieren:

1. Fälle, bei denen Obduktion und Reaktion nicht stimmen.

(*a*) Positive Reaktion bei negativem (oder zweifelhaftem) Sektionsbefund: 2 Fälle.

Von den 111 Fällen mit negativem Sektionsbefunde waren 109 auch probatorisch negativ, nur bei 2 Fällen hatte eine positive Reaktion stattgefunden und zwar erstens bei dem schon in der erwähnten Publikation ausführlich besprochenen H. I., welcher gar keine makroskopischen Herde, aber Adhäsion der linken Lunge und Hyperplasie zahlreicher Lymphdrüsen aufwies.

Der zweite Fall betrifft einen 10 jährigen Knaben, welcher sekundäre Tuberkulinreaktion gab.

Friedrich C. 143. Impfung am 5—9—'07 negativ, Wiederholung am 6—9 positiv; nach 24 Stunden undeutlich, nach 48 Stunden deutlich tastbare Papel von 6 mm. Durchmesser. 30—12 dritte Impfung; nach 24 Stunden 7, nach 48 Stunden 12 mm. Exitus am 4—1—'08. Obduktion: Insuffizienz der Mitral- und Aortenklappe nach rekruszierender Endokarditis. . . . Embolie der beiden Arteriae cerebrales mediae. . . . Infarkte der Milz und beider Nieren. Stauung in Leber, Milz und Nieren. Pericarditis mit hämorrhagisch fibrinösem Exsudat und partieller Verlötung des Herzbeutels mit dem Herzen im Bereiche des rechten Ventrikels. Bei mikroskopischer Untersuchung zahlreicher Schnitte von verschiedenen Stellen des Herzbeutels und von mehreren Lymphdrüsen aus der Bifurkation konnte keine Tuberkulose nachgewiesen werden.

In beiden Fällen ist nach meiner Meinung das Sektionsresultat nicht vollkommen deutlich.

(*b*) Negative Reaktion bei positivem Sektionsbefund: 29 Fälle.

Von den 89 Fällen, welche bei der Sektion Tuberkulose ergaben, zeigten 59 positive Reaktion schon bei der ersten Impfung.

Bei 7 Fällen erschien die Reaktion erst bei der Wiederholung der Impfung; (sekundäre Reaktion) unter diesen waren 4, bei denen Tuberkulose als Nebenbefund konstatirt wurde und 3 Fälle von tötlicher Tuberkulose. Die Adhäsionen der Lunge in dem einen, des Herzbeutels in dem anderen Falle sind jedenfalls als tuberkuloseverdächtig zu bezeichnen.

P. Josef, Nr. 155, eindreiviertel Jahre alt, mit Meningitis tuberculosa aufgenommen, 11—2. Impfung, am nächsten Tage keine Reaktion; Nun wird durch F. Hamburger 10 mg. Tuberkulin injiziert, welches positive Reaktion ergiebt, gleichzeitig zeigt sich nun auch (nach 48 Stunden) eine schwache kutane Reaktion (9 mm.) Bei täglicher Wiederholung verstärken sich die Reaktionen, ganz entgegengesetzt den sonstigen Erfahrungen bis zu 13 mm. Erst 2 Tage vor dem Tode sinkt die Reaktionsfähigkeit ab.

Aehnlich verhielt sich ein 6 monatliches Kind, welches 25 Tage vor dem Tode negative Tuberkulinreaktion gab, 2 Tage später auf Injektion von 0.01 mg. aber Stichreaktion zeigte. Nach weiteren 2 Tagen wurde die Kutanreaktion nochmals ausgeführt und die Einwirkung des Tuberkulins durch ein Pflaster verstärkt. Darauf zeigte sich eine deutlich tastbare Papel von 14 mm. Durchmesser.

A. Max, Nr. 148. Klinische Diagnose: Lungentuberkulose und Hauttuberkulide. Obduktionsbefund: Chronische und subakute Tuberkulose beider Lungen und zahlreicher Lymphdrüsen; miliare Tuberkel in der Leber, Milz, den Nieren und in der Umgebung der Lungenherde.

Am interessantesten ist folgender Fall, welcher sich von ersten Lebenstage an bis zum Tode in der Säuglingsabteilung befand und bei dem mit grösster Wahrscheinlichkeit eine Infektion intra partum angenommen werden konnte. Die erste kutane Reaktion, 23 Tage vor dem Tode war negativ, die zweite, 7 Tage vor dem Tode, schwach positiv.

B. Alois, Nr. 188. Im Alter von 3 Stunden als kräftiges Kind aufgenommen. Die Mutter starb kurz nach der Geburt an Tuberkulose. Vom Alter von 7 Wochen an fieberte das Kind fortwährend und starb mit 3 Monaten. Bei der Sektion fand sich eine chronische Tuberkulose des lymphatischen Apparates und der Rachentonsillen, am stärksten betroffen waren die tracheobronchialen Lymphdrüsen. Ausserdem subakute miliare Tuberkulose einschliesslich der Meningen.

Die Fälle mit Tuberkulose als Nebenbefund, bie denen sekundäre Reaktion gefunden wurde, sind sämmtlich in der ersten Serie beschrieben worden. Bei zweien von ihnen (G. Elisabeth, Nr. III. und M. Anna, Nr. IV., halte ich es nicht für ausgeschlossen, dass zwischen den weit auseinander liegenden Prüfungen eine tuberkulöse Infektion stattgefunden hat. Nur der 5 jährige H. B. Nr. IX., bot keinen für torpide und sekundäre Reaktion typischen Sektionsbefund.

Der 4. Fall, H. Friderike, Nr. 63, ist nicht als echte Sekundärreaktion aufzufassen, sondern das Fehlen der Reaktion bei der ersten Prüfung ist auf die damals bestehende Masernerkrankung zu beziehen. In der gleichen Weise erklären sich zwei Fälle der nächsten Gruppe: negative Reaktion bei Tuberkulose als Nebenbefund, für welche ich in der ersten Publikation keine Erklärung geben konnte.

G. Leopoldine, 20 Monate, Nr. VIII. Negative Reaktion am 14., 13., und 12. Tage vor dem Tode. Es waren dies der 6—8te Tag nach dem Masernexanthem. Ebenso war bei Grete D. die zweimalige negative Reaktion 2 und 4 Tage nach dem Masernexanthem angestellt worden. Hieher gehört ein neuer Fall.

B. Joseph, drei und dreiviertel Jahre, Nr. 149. Kutane Reaktion 1 und 2 Tage nach dem Masernexanthem negativ, Tod an Bronchopneumonie 3 Tage später. Bei der Obduktion finden sich ausserdem bindegewebsartige Adhäsionen der rechten Lunge, in ihrer Spitze eine haselnussgrosse chronische Kaverne mit kalkigem Inhalt . . . Kalkige Herde in einzelnen regionären Lymphdrüsen . . . im Ausheilen bekriffene kleine tuberkulöse Geschwüre im Cœcum.

Zwei Fälle mit einmaliger negativer Reaktion bleiben ungeklärt; es ist wahrscheinlich, dass sie unterempfindliche Fälle waren, welche bei zweimaliger Impfung oder bei Injektion positiv reagiert hätten. Meine damalige Annahme, dass die mangelnde Reaktion durch Kachexie zu erklären sei, ist übrigens nicht ganz von der Hand zu weisen, da auch bei Tuberkulose als Nebenbefund eine kachektische Abnahme der Reaktionsfähigkeit vorkommt.

Z. Rudolph, Nr. 140, 2 Jahre, 3 Monate alt, mit Empyem aufgenommen; auf 4 Impfungen, welche 6—2 Tage vor dem Tode vorgenommen wurden, ergab sich nur bei dem ersten eine flache, nicht tastbare, aber intensiv rote, 10 mm. breite Reaktion; die anderen blieben vollkommen negativ, ebenso die 2 Tage vor dem Tode vorgenommene Injektion von 0.1 mg. Sektion: Empyem, Lobulärpneumonie, chronische Tuberkulose zahlreicher Lymphdrüsen, eine erbsengrosse Kaverne im Oberlappen, akute Miliartuberkulose des Peritoneums, vereinzelte stecknadelkopfgrosse Tuberkel von grauer Farbe in einigen mesenterialen Lymphdrüsen und in der Milz.

Die 18 Fälle, in welchen Tuberkulose als Todesursache bei negativer Reaktion gefunden wurde, sind 13 Fälle von miliarer und 5 Fälle von nicht miliarer Tuberkulose. Die Fälle mit nicht miliarer Tuberkulose wurden alle nur einmal 9—2 Tage vor dem Tode geimpft. Die negativen Fälle bei Miliartuberkulose wurden 12—2 Tage vor dem Tode der ersten Prüfung unterzogen; ich werde später durch den Vergleich mit jenen Fällen, bei welchen eine sukzessive Abnahme der Reaktionsfähigkeit im Verlaufe des Endstadiums nachgewiesen werden konnte, meine Erklärung rechtfertigen, dass die negative Reaktion hier als ein prämortales Erlöschen aufzufassen ist.

Von den 32 Fällen, welche keine vollständige Uebereinstimmung zwischen Sektionsbefund und Tuberkulose gaben, sind somit wahrscheinlich 18 als Erlöschen der Reaktionsfähigkeit zu deuten, 6 als geringe Empfindlichkeit

bei der ersten Applikation, welche bei der weiteren kutanen Impfung positiv wurde oder durch die Stichreaktion aufgedeckt wurde, oder bei weiterer Impfung aufgedeckt worden wäre (2 Fälle). Vier Fälle waren bei der Impfung in Folge der gleichzeitigen Masernerkrankung negativ. Bei zwei Fällen endlich, welche positives Impfresultat bei zweifelhaftem Obduktionsbefund darboten, ist die Möglichkeit eines Nachweises durch den Tierversuch versäumt worden.

2. Fälle, in denen Obduktionsbefund und Reaktion stimmt.

(a) Negative Reaktion bei negativem Befunde.

Bei den 109 Fällen dieser Kategorie wurden sechs verschiedene Todesursachen gefunden. Man kann also von allen diesen Krankheiten mit Sicherheit sagen, dass sie keine Tuberkulinempfindlichkeit bedingen.

Die Todesursachen waren folgende:

Pneumonie, Pleuritis, Empyem, 51; Meningitis cerebrospinalis, 19; Diphterie, 8; Sepsis, 5; Scharlach und Scharlach-Nephritis, 3; Leukämie und perniziöse Anämie, 3; je ein Kind starb an Tetanie, Encephalitis, akuter gelber Leberatrophie, Invagination und Frühgeburt. Unter den an Pneumonie und Enteritis verstorbenen Kindern waren 6 mit florider hereditärer Lues. Von diesen Fällen wurden 30 einmal, 12 zweimal, 7 dreimal, 2 viermal, 4 fünfmal, 2 sechsmal, 1 siebenmal und einer zehnmal geprüft. Man kann daraus in Uebereinstimmung mit den Befunden Hamburgers über die Stichreaktion den Schluss ziehen, dass die Tuberkulinimpfung an sich bei nicht Tuberkulösen keine Empfindlichkeit gegen Tuberkulin bewirkt.

(b) Positive Tuberkulinreaktion mit positivem Sektionsbefunde:

Diese Fälle sind einzuteilen in solche, bei denen Tuberkulose als Todesursache und solche, bei denen sie als Nebenbefund gefunden wurde, die ersteren wieder in Fälle mit Miliartuberkulose und in solche ohne miliare Aussaat.

Von den Fällen mit Tuberkulose als Nebenbefund sind 5 bereits in der ersten Serie besprochen worden. Von ihnen ist nur H. Anna 100 nochmals zu erwähnen, welche wie früher Nr. 140 den Beweis giebt, dass eine schwere Kachexie, auch ohne dass die Tuberkulose deren Grundlage bildet, kachektische Reaktionen verursachen kann. Ferner ist zu bemerken, dass die in der ersten Publikation geäusserte Vermutung, das plötzliche Verschwinden der Reaktionsfähigkeit bei P. Johann, Nr. 84, sei durch den Eintritt der Masern zu erklären, eine gesetzmässige Bestätigung gefunden hat.

In demselben Sinne ist der Verlauf der Reaktion bei den nächsten beiden Fällen zu deuten.

P. Stephan, Nr. 199 drei Jahre alt, mit Hirntumor aufgenommen. Acht Untersuchungen zwischen 26—11 1907 und 13—4 1908, ergeben starke Papeln. Dann erfolgen 6 negative Reaktionen während der Masern; am letzten Tage vor dem Tode erscheint wieder eine schwache Reaktion von

4 mm. Durchmesser. Sehr eigentümlich ist, dass während alle früheren Reaktionen innerhalb 24 Stunden eingetreten waren, diejenigen vom 2—4 und 13—4 einen torpiden Verlauf nahmen. Die vom 2—4 war nach 48 Stunden 10, nach 3 Tagen 10; die vom 13—4 war nach 24 Stunden negativ, nach 48 Stunden stark positiv, 12 mit Ausläufern, später intensiv violett. Exitus am 29—4. Diffuse eitrige Entzündung des perioesophagealen und retropharyngealen Gewebes und des vorderen Mediastinums. Ein apfelgrosser käsiger Tuberkel im Kleinhirn. Chronischer innerer Hydrocephilus . . . chronische Tuberkulose zahlreicher Lymphdrüsen, totale adhäsive Pleuritis rechts, ein ringförmiges, tuberkulöses Darmgeschwür.

D. Johann, Nr. 186. Aufgenommen mit Skrofulose. Reaktionen am 31—12 und 12—2 sehr intensiv. Hausinfektion mit Masern. Vom 2. bis 20. März tägliche Impfung; die Reaktion schwächt sich bis zum Nullpunkte ab, steigt dann wieder an und verläuft in wechselnder Intensität bis zum Tode am 21—3. Sektionsbefund: Akute Enteritis des Dickdarms, diffuse, eitrige Peritonitis und Bronchitis. . . Einige über hanfkorngrosse, zum Teil verkäste Tuberkel in den rechten tracheobronchialen Lymphdrüsen und fast vollständige Verkäsung einer kleinerbsengrossen bronchopulmonalen Lymphdrüse am linken Lungenhilus. 2 stecknadelkopfgrosse, graue, verkäste Tuberkel im rechten Oberlappen.

Von den übrigen Fällen erwähne ich nur die Sektionsbefunde, soweit sie die Grundlage der positiven Kutanreaktion bildeten.

V. Karl, 6 Jahre alt, Nr. 124. Encephalitis, 18—9. Kutanreaktion 9 mm. 27—9 quantitative Reaktion; bei unverdünntem und 25% Tuberkulin entstehen Blasen im Mittelpunkte bis zu 20 mm. durchmessender Papeln, am 2—10 entstehen noch ausgedehntere Reaktionen (bis 28 mm.). Bei der Obduktion am 8—10. findet sich nur ein erbsengrosser, verkreideter subpleuraler Knoten an der Spitze des linken Unterlappens und verkäste Lymphdrüsen an der Bifurkation.

S. Joseph, Nr. 190, 6 Jahre alt. Herztod nach Diphtherie. Hyperplasie des lymphatischen Apparates in Mund- und Rachenhöhle und der mesenterialen Lymphdrüsen. Ein hanfkorngrosser verkreideter Herd in einer tracheobronchialen Lymphdrüse und akute miliare Tuberkel in derselben und einigen benachbarten Lymphdrüsen. Adhäsive Pleuritis des rechten Unterlappens.

Sch. Alois, Nr. 173, 2 Jahre alt. Empyem nach Scharlach. Chronische Tuberkulose zahlreicher Lymphdrüsen, ein narbig geschrumpfter Plaque im Dünndarm, vereinzelte stecknadelkopfgrosse Tuberkel in Milz und Lungen.

Sch. Emilie. Vitium Cordis. Mässige Hyperplasie der Gaumen- und Rachentonsillen, Verkäsung zahlreicher Lymphdrüsen.

B. Berta, Nr. 131, 6 Jahre. Bei der ersten Impfung am 6—9. schwache Reaktion, die sich bei den weiteren Impfungen bis zu 18 mm. verstärkt. Tod an eitriger Peritonitis, daneben zahlreiche tuberkulöse Veränderungen. Kaverne, Pericarditis, Tuberkulose vieler Lymphdrüsen.

Miliartuberkulose und Meningitis Tuberculosa.

Von den 30 Miliartuberkulosen sind 14 bei der ersten Serie besprochen worden. Diesmal habe ich mein Hauptaugenmerk darauf gelenkt, durch

tägliche Impfung während des ganzen Verlaufes der Miliartuberkulose ein genaues Bild über die Abnahme der Reaktionsfähigkeit zu erhalten. Allerdings wird durch die Impfung das Bild wieder einigermassen in der Richtung beeinflusst, dass die schon schwindende Reaktionsfähigkeit wieder angeregt wird. Besonders ist dies bei jüngeren Kindern beobachtet worden, wie ich noch später ausführen werde. Charakteristisch für die Reaktion im Endstadium ist das wechselnde Verhalten in der Farbe und Tastbarkeit der Papeln. Aehnlich wie die fliegende Röte im Gesichte und die Trousseau'schen Flecken sind die Papeln manchmal durch einige Stunden sichtbar, um dann wieder für längere Zeit, manchmal für Tage zu verschwinden, und gelegentlich wieder aufzuflackern. Manchmal sieht man um die Impfstellen flache anämische Höfe, manchmal farblose Erhabenheiten, welche nur dem tastenden Finger bemerkbar werden. Im Gegensatze dazu kommen wieder ganz scharfrandige Hyperämieen vor. Ein charakteristisches Beispiel für das Verhalten bei täglichen Impfungen bietet der folgende Fall.

Z. Anna, 11 Jahre, 9 Monate, Nr. 160. Krankheitsbeginn vor 3 Wochen. Aufnahme am 14—2. Tägliche Impfung bis 25—2. Tod am 26—2. In den ersten 6 Tagen sehen wir starke Papeln von 9—12 mm. Durchmesser, welche in intensiv violette Pigmentierung übergehen. Vom 20 - 22—2. entstehen undeutlich tastbare Papeln von zartrötlicher Farbe. Am 24—2, zwei Tage vor dem Tode, verstärken sich die Papeln wieder an Ausdehnung und Tastbarkeit. Erst am Todestage verlieren die Reaktionen ihre Tastbarkeit völlig. Sie sind von blass-violetter Farbe.

In dem folgendem Fall ist die Kachexie viel schärfer ausgesprochen.

G. Leopoldine, Nr. 199. Ein Jahr alt. Erste Untersuchung am 13—3., dann tägliche Impfungen vom 16—3. bis zum Tode am 25—3. Schon die erste Reaktion 15 Tage vor dem Tode ist kachektisch. 10–8 Tage vor dem Tode ist die Reaktion undeutlich tastbar und farblos. 5 Tage ante mortem, wird aber nicht nur die letzte, sondern auch zwei frühere wieder tastbar; vom nächsten Tage an erlischt die Reaktion völlig; um den Kratzeffekt sind nur anämische Höfe zu sehen, während die älteren Reaktionen als scharf begrenzte livide Flecke deutlich sichtbar bleiben.

In anderen Fällen ist die Abnormität nicht durch die Tastbarkeit, sondern durch die eigentümlichen Farbenunterschiede gekennzeichnet.

B. Robert, Nr. 178. Zwei Jahre und drei Monate, Aufnahme 2 Wochen nach Krankheitsbeginn in kräftigem Zustande. Vom 16—3. bis zum Todestage am 23—3, tägliche Untersuchung. Gute Papelbildung, aber die Farbe variirt zwischen hochrot, livid und farblos.

Ausnahmsweise bessert sich sogar die Reaktionsfähigkeit im Verlauf der Meningitis, ohne dass daraus irgend ein prognostischer Schluss gezogen werden könnte.

D. Otto, 2 Jahre alt, kräftig. Impfungen am 11 und 12—2 (12 und 11 Tage A.M.) geben nur undeutliche Flecke. 10 Tage A.M. Injektion von 1

mgr. (durch Hamburger) positive Stichreaktion. 6—1 Tage A.M. weitere Impfungen. Die Impfung 6 A.M. bewirkt einen hellroten Fleck von 25 mm. Durchmesser, der am nächsten Tage schon wieder verschwunden ist, aber dann wieder aufflackert. Die weiteren Impfungen ergeben bald nichts, bald nur undeutliche Flecke.

Hier mag die Tuberkulinreaktion zur Verstärkung beigetragen haben, wie in dem früher erwähnten Falle; das tritt aber nicht immer ein.

F. Karl, Nr. 151, 7 Jahre alt. Meningitis mit über zweimonatlichem Verlaufe. 10 Tage A.M. Impfung, ganz undeutlicher Fleck. In den nächsten Tagen mehrmals Injektion von Tuberkulin, bis zu 2 mgr., trotzdem weder Auftreten einer Stichreaktion noch auch Auftreten kutaner Reaktionen.

Dass die Abnahme der Reaktionsfähigkeit bei Miliartuberkulose keineswegs alle Fälle betrifft, habe ich schon bei der ersten Serie erwähnt, und der folgende Fall bietet ein gutes Beispiel dafür. Hier wurde die einzige Impfung 2 Tage ante mortem ausgeführt, von einem sekundären Verstärken der Reaktion kann also nicht die Rede sein.

St. Johann, Nr. 122, 11 Monate alt, am 1—10. quantitative Impfung mit Tuberkulin 1 zu 1, 16, 64 Kontrolle. Nach 24 Stunden bei 1 starke Papel (15.8 mm.), bei 4 undeutliche Papel (20:9). bei 16, 4 und 64 Kontrolle negativ.

Nichtmiliare Tuberkulose als Todesursache.

Der Verlauf der Reaktionsfähigkeit zeigt keine prinzipielle Verschiedenheit von der miliaren Tuberkulose mit Ausnahme dessen, dass hier die kachektische Form eher zu beginnen scheint. Ein gut beobachtetes Beispiel in dieser Richtung ist folgender Fall:

P. Margarethe, Nr. 109. Geboren am 17—1—'07, am 11—5 wegen eines lupusartigen Geschwüres der rechten Wange zum ersten Male untersucht. Positive Reaktion, ebenso am 12., 14., 17. Juli, und am 6. Juli. Letztere Probe ergiebt nach 24 Stunden 16, nach 48 Stunden 10, ist aber nach 3 Tagen fast verschwunden. Am 15—7, quantitative Impfung 1—10—100—1000. Nur beim unverdünnten Tuberkulin vorübergehender flacher Fleck von 12 mm. Am 27—7. Exitus. Allgemeine Tuberkulose, welche möglicher Weise von dem Ulkus der rechten Wange als Primäraffekt ausgegangen war.

Hier war also schon 12 Tage vor dem Tode die Reaktionsfähigkeit erloschen, während in dem folgendem Falle, der nach Alter und Todesart ganz ähnlich war, noch 4 Tage vor dem Tode eine abnorm starke Reaktion vorhanden war.

L. Alfred, Nr. 101. 7 Monate. Bronchialdrüsentuberkulose. Erste Prüfung im 5. Lebensmonate. Reaktion positiv, 2te Prüfung am 5—7 mit unverdünntem oder 25% Tuberkulin; nach 24 Stunden starke Papeln von 30 und 27 mm. Durchmesser, welche ihre Tastbarkeit bis zum Tode behalten und nur von der anfänglich hochroten Farbe zu einer cyanotisch schmutzigen Verfärbung übergehen.

Auch bei kachektischen Kindern mit Lungentuberkulose kann sich die Reaktion lange Zeit erhalten, so dass man zu falschen Schlüssen gedrängt

würde, wenn man aus der positiven Reaktion eine gute Prognose stellen würde.

S. Marie, 3 Jahre, Nr. 161. Kachektisches Kind, seit 2 Jahren kränklich, seit 4 Monaten Sputum, Kavernensymptome. In dem letzten Monate vor dem Tode 16 Untersuchungen, bis zu 21 A.M. sind die Reaktionen immer deutlich tastbar, 8–17 mm. gross und verlieren nur rasch ihre Farbe. 20–17 A.M. sind die Papeln undeutlich und von schmutzig-roter Färbung. Dann finden wir wieder 13–7 A.M. sehr starke Papeln von 7–12 mm. Durchmesser. Erst jetzt schwächt sich die Reaktion ab, aber noch am Todestage selbst ist die Probe des Vortages zu einem deutlich sichtbaren Fleck von 10 mm. geworden . . . Bei der Sektion findet sich schwerste allgemeine Tuberkulose und speziell eine kindsfaustgrosse Kaverne im linken Oberlappen.

Zur Darstellung der Abschwächung der Reaktionsfähigkeit vor dem Tode habe ich alle an Tuberkulose verstorbenen Kinder auf einer Tabelle vereinigt. Die eingezeichneten Reaktionsgrössen beziehen sich auf die je 24 Stunden vorher ausgeführten Impfungen.

Absolut keine Abschwächung zeigten die Fälle 2, 47, 52, 57, 67, 60, 66, alles Kinder zwischen 6 Monaten und 2½ Jahren; deutliche Abschwächung im Verlaufe der Untersuchung wiesen auf 1, 4, 6, 9, 16, 21, 27, 30, 47, 50. Das jüngste der Kinder war ½ Jahr alt, alle übrigen standen zwischen 3 und 11 Jahren. Das Durchschnittsalter der zweiten Gruppe betrug 6.3 Jahre.

Drei Kinder zeigten sogar eine Zunahme der Reaktions-Fähigkeit im Verlaufe der Untersuchung (8, 13, 15); sie standen im Alter von 3, 6, 3 Monaten; wenn wir diese Kinder mit der ersten Gruppe vereinigen, ergiebt sich für jene Fälle, welche keine Tendenz zur Abnahme zeigen, ein Durchschnittsalter von 11.1 Monaten.

Diese Differenz muss darauf führen, dass das Lebensalter auf die Reaktionsfähigkeit einen grossen Einfluss nimmt.

Zu demselben Resultat kommen wir, wenn wir die Säuglinge (bis zu einem Jahre) und die älteren Kinder (zwischen 7 und 14 Jahren) einander gegenüber halten.

Von 16 Kindern des ersten Lebensjahres (darunter 6 Miliartuberkulosen) zeigte nur eines eine sichere Abschwächung; drei reagierten primär negativ, zwei schwach positiv; von diesen 5 wurden 3 weiter geimpft und fingen wieder zu reagieren an. Die übrigen zeigten kräftige primäre Reaktion. Auffallend war besonders, dass mehrere (52, 57, 66) noch in den letzten Tagen vor dem Tode sehr stark reagierten.

Von 17 Kindern zwischen 7 und 14 Jahren (darunter 13 Miliartuberkulosen) zeigten 12 kachektischen oder negativen Erfolg, nur 4 boten deutlich tastbare Reaktionen bis zu 4, 7, 9, 7 Tagen ante exitum.

Wenn wir noch daran denken, dass nach den Angaben zahlreicher Autoren die Erwachsenen im 3. Stadium der Lungentuberkulose sehr

ÜBERSICHT ÜBER DIE REAKTIONSFÄHIGKEIT ALLER AN TUBERKULOSE VERSTORBENEN KINDER.

	Jahre.	Monate.	Die Zahl bedeutet die Ausdehnung der Papel in mm., das Zeichen ⌒ deutlich, ~ undeutlich, — nichttastbar.	Tage vor dem Tode.												
				12	11	10	9	8	7	6	5	4	3	2	1	
1. P. Margarete	..	6	77, 45, 43, 40 Tage a. m. stark positiv 12 a. m. $\overline{v}$.	..	..	..	..	..	..	..	..	..	..	..	..	Miliar.
2. E. Karl	2	6	61, 55 (15–25), 48, 35, 26 Tage a. m.	..	..	..	..	..	..	..	..	..	..	..	..	..
3. K. Gustav	..	10	Stark positiv, dann 21, 19 a. m. Anergie durch Masern. 45, 25, 19, 13 Tage a. m. positiv ($\widehat{12}$–$\widehat{7}$).	$\widehat{11}$	$\widehat{10}$	$\widehat{14}$	$\widetilde{16}$	$\widetilde{16}$	$\widetilde{12}$	$\widehat{9}$	$\widehat{10}$	$\widehat{13}$	$\widetilde{10}$	$\widehat{14}$	..	..
4. W. Franz	5	6	43, 33, 32, 31, 30 T. a. m. positiv 29–19 Anergie durch 12 Masern.	..	..	$\widetilde{4}$	$\widetilde{4}$	..	..	..	..	$\widetilde{7}$	v	..	$\overline{v}$	..
5. P. Marie	2	..	35 T. $\widehat{15}$.	..	..	..	..	..	..	..	..	..	..	..	..	..
6. Sch. Hedwig	7	..	34 T. $\widehat{20}$, 18 T. $\widehat{13}$, 14, T. $\widehat{7}$.	..	..	..	..	..	..	..	..	$\overline{6}$	..	..	..	Miliar.
7. V. Elisabeth	..	4	33 T. $\widehat{10}$.	..	..	..	..	..	..	..	..	..	..	..	..	"
8. W. Johann	..	3	31 T. 4 Schw. pos. $\widehat{6}$, 14, $\widehat{8}$.	..	..	..	..	$\widetilde{10}$	..	..	..	..	..	..	..	"
9. Sch. Marie	3	..	28–21 T. zw. $\widehat{8}$ u. $\widehat{17}$, dann schwächer, dann wieder stärker 13 T. $\widehat{19}$.	..	..	..	$\widehat{10}$	$\widehat{15}$	$\widetilde{8}$	..	..	..	..	$\overline{10}$	$\overline{10}$	..
10. B. Therese	..	5	27 T. $\widetilde{7}$.	..	..	..	..	..	..	..	..	..	..	..	..	..
11. R. Marie	12	..	26 T. $\widetilde{10}$.	..	..	..	..	..	..	..	..	..	..	..	..	..
12. P. Franz	..	5	25 T. $\widehat{6}$.	..	..	..	..	..	..	..	..	..	..	..	..	..
13. A. Max	..	6	25 T. v. 23 $\widetilde{v}$. 21 Ph. Pfl. $\widehat{11}$ (nach Injektion).	..	..	..	..	..	..	..	..	..	..	..	..	..
14. G. Emilie	..	11	24 T. $\widehat{10}$.	..	..	..	..	..	..	..	..	..	..	..	..	..
15. B. Alois	..	3	23 T. v.	..	..	..	$\widetilde{5}$	..	..	..	..	..	..	..	..	Miliar.
16. F. Rudolph	5	..	21 T. $\widehat{9}$, 18, T. $\widetilde{7}$ 15 T. $\widetilde{6}$.	$\widetilde{3}$	..	..	v	..	..	..	..	..	..	..	..	"
17. M. Friedrich	1	9	15 T. $\widehat{15}$.	..	..	..	..	..	..	..	..	..	..	..	..	"
18. B. Leopold	..	12	14 T. 10.	..	..	..	..	..	..	..	..	..	..	..	..	"

19. Sch. Anna	..	3	14 T. 11.	..	6	..	..	..	..	..	..	..	..	..	..	..	..	..
20. J. Josefa	..	7	.....	..	v	..	8	..	..	..	v	..	..	..	..	..	..	..
21. Z. Anna	11	9	.....	9	10	11	5	4	12	7	9	13	..	13	5	Miliar.		
22. B. Otto	..	2	Inj. 1 mgr. A. M. 10. Tg.	v	v	..	..	..	..	25	v	10	15	13	v	..		
23. St. Franz	..	5	.....	..	7	..	..	..	..	..	..	..	..	..	..	..		
24. M. Marie	..	6	.....	v	..	..	v	..	..	..	..	..	..	..	..	Miliar.		
25. S. Sophie	..	10	.....	..	13	..	..	..	..	..	..	10	..	..	..	"		
26. J. Leopoldine	..	12	.....	..	4	..	..	..	v	..	..	..	..	..	..	"		
27. K. Willibald	..	9	.....	..	11	..	..	..	13	..	..	..	..	v	..	"		
28. N. Hedwig	1	3	.....	..	..	4	..	..	..	..	..	..	..	..	..	"		
29. F. Karl	7	..	.....	..	..	v	..	v	v	..	..	r	..	..	..	"		
30. G. Leopoldine	10	..	.....	..	..	..	7	5	7	7	6	v	..	v	v	"		
31. F. Adolf	1	11	.....	..	..	..	10	..	..	..	..	..	..	..	..	"		
32. St. Franz	1	2	.....	..	..	..	7	..	..	..	..	..	..	..	..	"		
33. K. Marie	8	..	.....	..	..	..	10	..	..	..	..	..	..	..	..	"		
34. K. Victor	6	..	.....	..	..	..	v	v	..	..	..	..	..	..	..	"		
35. Sp. Georg	5	..	.....	..	..	..	v	..	..	..	..	..	..	..	..	..		
36. S. Leopoldine	1	2	.....	..	..	..	..	10	..	..	11	..	..	..	..	Miliar.		
37. R. Hermine	3	..	.....	..	..	..	..	10	..	..	..	..	..	..	..	"		
38. G. Therese	..	9	.....	..	..	..	..	4	..	..	..	..	..	..	..	"		
39. H. Marie	13	..	.....	..	..	..	..	5	..	..	..	..	..	..	..	"		
40. K. Adele	4	..	.....	..	..	..	..	v	..	..	..	..	..	..	..	"		
41. P. Josef	1	9	.....	..	..	..	..	9	..	5	4	8	13	4	..	"		
42. St. Karoline	..	9	.....	..	..	..	..	..	v	..	..	..	..	..	..	..		
43. T. Eny	2	..	.....	..	..	..	..	..	v	..	..	..	..	..	..	Miliar.		
44. H. Johann	8	..	.....	..	..	..	..	..	v	..	..	..	..	..	..	..		
45. S. Josefine	7	..	.....	..	..	..	..	..	10	..	..	..	5	..	..	Miliar.		
46. H. Emil	5	6	.....	..	..	..	..	..	v	..	..	..	..	..	..	"		

ÜBERSICHT ÜBER DIE REAKTIONSFÄHIGKEIT ALLER AN TUBERKULOSE VERSTORBENEN KINDER.

	Jahre.	Monate.	Die Zahl bedeutet die Ausdehnung der Papel in mm., das Zeichen ⌒ deutlich, ~ undeutlich, — nichttastbar.	Tage vor dem Tode.												
				12	11	10	9	8	7	6	5	4	3	2	1	
47. B. Robert	2	3	.....	..	..	..	..	..	⌒10	..	⌒12	⌒9	⌒13	⌒9	..	Miliar.
48. M. Agnes	6	..	.....	..	..	..	..	..	..	8	..	..	..	..	..	..
49. B. Marie	7	..	.....	..	..	..	..	..	..	v	..	..	..	..	..	..
50. D. Anna	5	..	.....	..	..	..	..	..	..	..	~10	~9	v	v	..	Miliar.
51. B. Leopoldine	4	..	.....	..	..	..	..	..	..	..	..	v	..	..	..	"
52. L. Alfred	..	7	.....	..	..	..	..	..	..	..	..	⌒30	..	..	..	..
53. D. Konrad	4	6	.....	..	..	..	..	..	..	..	..	..	v	..	v	Miliar.
54. K. Alois	..	3	.....	..	..	..	..	..	..	..	..	..	~r	v	..	"
55. W. Karoline	5	6	.....	..	..	..	..	..	..	..	..	..	v	..	..	"
56. R. Max	..	1	.....	..	..	..	..	..	..	..	..	..	v	v	..	"
57. C. Valerie	..	6	.....	..	..	..	..	..	..	..	..	..	⌒20	..	..	"
58. Z. Anna	1	6	.....	..	..	..	..	..	..	..	..	..	~5	..	..	"
59. K. Amalie	1	6	.....	..	..	..	..	..	..	..	..	..	11	..	..	"
60. L. Oskar	..	6	.....	..	..	..	..	..	..	..	..	..	⌒8	..	..	..
61. L. Valerie	9	..	.....	..	..	..	..	..	..	..	..	..	..	v	..	Miliar.
62. D. Leopoldine	9	..	.....	..	..	..	..	..	..	..	..	..	..	v	..	"
63. C. Anton	3	..	.....	..	..	..	..	..	..	..	..	..	..	r	..	..
64. I. Leopoldine	1	3	.....	..	..	..	..	..	..	..	..	..	..	9	..	Miliar.
65. M. Stefanie	1	9	.....	..	..	..	..	..	..	..	..	..	..	~13	..	"
66. St. Johann	..	11	.....	..	..	..	..	..	..	..	..	..	..	⌒15	..	"
67. P. Aloisa	1	10	.....	..	..	..	..	..	..	..	..	..	⌒10	⌒12	..	"

häufig, ja fast regelmässig negative Reaktion schon lange vor dem Tode geben, so kommen wir zu dem Schlusse, dass die Reaktionsfähigkeit auf Tuberkulin um so länger gegen den Exitus hinaus erhalten bleibt, je jünger die Individuen sind.

Der Wert der kutanen Probe erhöht sich dadurch wieder für das erste Kindesalter. Sie hat hier somit aus drei Gründen besonderen Wert:

Erstens, weil die Tuberkulose hier—gegenüber den älteren Altersstadien—nicht häufig vorkommt.

Zweitens, weil die Tuberkulose hier selten zu inaktiven Formen eingeengt wird, sondern progredient verläuft.

Drittens, weil die Reaktionsfähigkeit bis zu den letzten Tagen vor dem Tode andauert, also die Tuberkulinreaktion auch bei Meningitis und Miliartuberkulose verwertbar ist.

Wenn wir die Resultate der ersten 100 Sektionen mit den Resultaten des zweiten Hunderts vergleichen, so sehen wir, dass die Genauigkeit der Diagnose durch die zunehmende Uebung im Erkennen der Impfeffekte sich wesentlich verbessert hat. Während in der ersten Serie von 47 Tuberkulösen 17 probatorisch negativ gewesen waren, also 32%, wurden in der zweiten Serie nur sechs, d. i. 12% ohne Reaktion befunden. Durch genaue Kenntnis des Momentes, in welchem die Reaktionsfähigkeit verringert wird (Masern, letzte Stadien der Tuberkulose bei älteren Kindern), werden sich Fehlschlüsse aus dem negativen Ergebnisse fast vollständig vermeiden lassen.

Zusammenstellung aller Fälle nach dem Lebensalter.

(Siehe Tabelle.)

Hier tritt nun wieder die enorme Zunahme der Tuberkulosehäufigkeit, wie sie Müller, Franz Hamburger, Sluka u. a. durch die Zusammenstellung der Sektionsbefunde bewiesen haben, deutlich zu Tage. Während unter 21 Kindern des ersten Vierteljahres nur ein einziges tuberkulös befunden wurde, haben wir in der letzten Altersgruppe (10–14 Jahre) nur ein einziges, das keine Tuberkulose aufwies. Und auch dieses war vermutlich schon mit Tuberkulose in Berührung gekommen, denn es war jener Fall, der sekundäre Kutanreaktion bei fraglichem Obduktionsbefunde (pericardiale Adhäsionen) ergab.

Auffallend und wohl zufällig ist die hohe Zahl der Tuberkulose im zweiten Vierteljahre (5 unter 19 Fällen). Dieser Befund geht über die bei grösseren Untersuchungsreihen gefundenen Durchschnittszahlen hinaus.

Alle Zahlen sind viel höher, als die bei statistischer Prüfung der lebenden Kinder ermittelten; das kommt daher, dass die Tuberkulose in 67, also einem Drittel der Fälle selbst die Todesursache darstellte.

ZUSAMMENFASSUNG.

Übersicht über die 200 Fälle nach Reaktion und Sektionsbefund.

Sektionsbefund.	Kutane Reaktion.	Säuglinge im Alter von Monaten.			Kinder im Alter von Jahren.						Summe.
		0—3	3—6	6—12	0—1	1—2	2—4	4—6	6—10	10—14	
Keine Tuberkulose.	Negativ einmal geprüft (*a*).	19	12	17	48	13	9	5	5	..	80
	mehrmals geprüfte (*b*).	..	1	7	8	3	7	..	..	..	18
	durch Stichreakt. überprüft.	1	1	5	7	1	3	..	..	..	11
	Negativ dann positiv (*c*).	..	..	..	..	..	..	..	..	1	1
	Positiv (einmal gepr.) (*f*).	..	..	..	..	..	..	1	..	..	1
Tuberkulose als Todesursache ...	Negativ einmal gepr. (*a*).	..	..	1	1	1	2	5	4	..	13
	mehrmals gepr. (*b*).	..	..	..	..	1	1	..	3	..	5
	dann positiv (*c*).	1	..	1	2	1	..	..	..	..	3
	Positiv einmal gepr. (*f*).	..	4	6	10	7	2	1	2	3	25
	gleichbleibend (*g*).	..	1	1	2	2	2	..	..	1	7
	abnehmend (*h*).	..	..	1	1	..	1	2	4	3	11
	wechselnd (*i*).	..	..	..	..	..	2	1	..	..	3
Tuberkulose als Nebenbefund ...	Negativ einmal geprüft (*a*).	..	..	..	..	1	..	..	1	..	2
	mehrmals geprüft (*b*).	..	..	1	1	1	1	..	..	..	3
	dann posit. (*c*).	..	..	1	1	1	..	2	..	..	4
	Positiv einmal gepr. (*f*).	..	..	..	..	2	1	..	1	1	5
	gleichbleibend (*g*).	..	..	..	..	..	..	..	2	..	2
	abnehmend (*h*).	..	..	..	..	..	1	1	..	1	3
	wechselnd (*i*).	..	..	..	..	..	3	..	..	..	3
Summe aller Fälle.		21	19	41	81	34	35	18	22	10	200
Summe der Tuberkulösen.		1	5	12	18	17	16	12	17	9	89
Prozentsatz der Tuberkulösen.		5	26	29	22	50	46	67	77	90	45

	Resultat der Intravitalen Untersuchung.		Resultat der Obduktion.			
			Tuberkulose.			Keine Tuberkulose.	Summe.
			Todesursache.	Nebenbefund.	Summe Tuberkulose.		
a	negativ	einmal geprüft	13(1)	2(0)	15(1)	80(30)	85(31)
b		mehrmals geprüft	5(4)	3(1)	8(5)	18(17)	27(27)
c		durch Injektion (Franz Hamburger) überprüft	.....	.....	.....	11(10)	11(11)
d	zuerst neg. dann sekundär pos.		3(3)	4(0)	7(3)	1(1)	8(4)
e	positiv	einmal gepr.	25(10)	5(3)	30(13)	1(0)	31(13)
f		Reaktionsfähigkeit	7(5)	2(2)	9(7)	.....	9(7)
g		mehrmals gepr. abnehmend	11(7)	3(0)	14(7)	.....	14(7)
h		mehrmals gepr. wechselnd	3(3)	3(3)	6(6)	.....	6(6)
	In Klammern die Anzahl der Fälle der zweiten Serie		67(33)	22(9)	89(42)	111(58)	200(100)

Diese kolossale Häufigkeit der Tuberkulose erklärt sich damit, dass die Kinder aus Wien, einer mit Tuberkulose ganz besonders durchseuchten Stadt und aus armen Arbeiterbezirken stammen.

Schluss-Sätze.

1. Positiver Ausfall der kutanen Reaktion beweist mit Sicherheit das Vorhandensein tuberkulöser Veränderungen (66 sichere, 2 unsichere, keine negativen Obduktionsbefunde).

2. Negativer Ausfall beweist im allgemeinen das Freisein von Tuberkulose (109 negative Sektionsbefunde).

Es kommt aber auch vor, dass Tuberkulöse negativ reagieren und zwar geschieht dies:

(*a*) Gesetzmässig während der Masernerkrankung.

(*b*) Sehr häufig im letzten Stadium tötlicher Tuberkulose. Die Reaktionsfähigkeit versagt hauptsächlich bei älteren Kindern, seltener bei Kindern des ersten Lebensjahres.

(*c*) Ohne bekannte Ursache. Die letztere Form ist meistens auf eine geringe Empfindlichkeit gegen Tuberkulin begründet, welche sich durch Wiederholung der kutanen Probe (sekundäre Reaktion) oder durch Injektion von Tuberkulin (Stichreaktion) zu positiver Reaktionsfähigkeit steigern lässt.

Sie betrifft, wie sich aus den Untersuchungen an lebenden Kindern schliessen liess, vornehmlich ältere Kinder mit kleinen, inaktiven, tuberkulösen Herden, kommt jedoch ausnahmsweise auch bei jüngeren Kindern und solchen mit florider Tuberkulose vor.

Experimentos con la Reacción Cutánea de la Tuberculina en Docientos Niños Estudiados en la Mesa de Autopsias.—(VON PIRQUET.)

Primero se describe la ejecución de los diversos métodos modernos y las ventajas de la reacción cutánea comparada con la oftálmo- y dermo-reacción. De cerca de 1,600 niños que sirvieron para el experimento cutáneo en dos hospitales de Niños en Viena, 200 murieron y fueron disecados cuidadosamente. De éstos, 68 casos dieron reacción positiva; 66 mostraron tubérculos macroscópicos en la autopsia; el resultado de la disección fue incierto en dos casos únicamente; en uno de ellos se encontraron adhesiones del pericardio á la pleura. Por lo tanto se puede concluir que la infección tuberculosa existe cuando la reacción cutánea es positiva.

La reacción fué negativa en los siguentes:

(1) En los casos restantes (109) de autopsia negativa.

(2) En varios casos de tuberculosis fatal, particularmente en los niños mayores en los cuales la prueba se hizo pocos días antes de la muerte.

(3) En casos de tuberculosis complicados de sarampión.

(4) En algunos casos en que ninguna de la razones anteriores pudieron aducirse.

Como se dijo, de acuerdo con otros experimentos, ocurrió especialmente en casos en que la tuberculosis era leve y parecía inactiva. A menudo se produjo una reacción positiva secundaria en aquellos en que se hizo una segunda prueba cutánea ó segunda inyección de tuberculina.

Expériences faites sur 200 enfants avec la réaction tuberculine cutanée.—(VON PIRQUET.)

D'abord, description des différentes méthodes nouvelles et des avantages de la réaction cutanée sur les réactions ophtalmiques et hypodermiques. Sur environ 1,600 enfants des hôpitaux de Vienne, qui subirent le réaction cutanée, 200 moururent et furent soigneusement disséqués.

Sur ceux-ci, 68 cas montraient des signes d'une réaction positive, 66 avaient des tubercules macroscopiques; le résultat de la dissection n'était incertain que dans deux cas, dans l'un desquels on trouva une adhésion pleurétique du Pericarde. On conclut qu'un cas où la réaction cutanée était positive, peut être considéré comme tuberculeux.

On trouve une réaction négative dans les cas suivants:

(1) Dans tous les autres cas négatifs.

(2) Dans quelques cas de tuberculose fatale, particulièrement chez des enfants plu ágés, chez lesquels la méthode avait été appliquée seulement quelques jours avant la mort.

(3) Dans les cas tuberculeux compliquées de rougeole pendant l'emploi de la tuberculine.

(4) Dans des cas où aucune des causes susnommées ne pouvaient être données. (Spécialement dans les cas, comme on fut aussi le voir par d'autres expériences, où la tuberculose était légère et paraissait inactive; souvent, par une seconde réaction cutanée ou par l'infection de la tuberculine, une réaction secondaire positive fut constatée.)

Experience with the Cutaneous Tuberculin Reaction.—(VON PIRQUET.)

First the technic of the different new methods is described and the advantages of the cutaneous reaction in comparison with ophthalmo- and dermo-reaction stated. Of about 1600 children, who underwent the cutaneous proof in two children's hospitals of Vienna, 200 died and were carefully dissected.

Sixty-eight cases of them were found to be positive in the reaction.

Sixty-six of them showed postmortem macroscopical tubercles; in only two cases was the result of the dissection uncertain, in one of which was found a pleuritic adhesion of the pericardium. Therefore, one came to the conclusion that, from a positive cutaneous reaction, a tuberculosis infection can be inferred.

A negative reaction was found in the following: (1) In all (109) remaining cases of negative postmortem; (2) in several cases of fatal tuberculosis, particularly in older children, when the proof was made only some days before death; (3) in cases of tuberculosis when the proof was made during an attack of measles; (4) in some cases in which none of the above causes could be given. (It especially occurred in cases where the tuberculosis was slight and seemed inactive; often after a second cutaneous test or by injection of tuberculin a secondary positive reaction was obtained.)

DISCUSSION.

DR. WOODCOCK (Leeds, England) remarked that he had tried Calmette's conjunctival test in possibly more than 400 cases.

In several cases, especially in children, the test failed, owing to the spasm of the lids, nervousness on the part of the patient causing this, the result being the tuberculin was ejected as soon as it was introduced. Apart from this children over seven years of age reacted well to "Calmette," and accidents were few.

In several adults he met with regrettable incidents. Headache and slight fever, and undoubted local and general discomfort were not uncommon. Possibly these conditions might be lessened by special local attention. One

patient gave a brilliant reaction and threatened legal proceedings. This patient had trouble with his eye for three months.

In the case of the von Pirquet reaction, Dr. Woodcock would like to hear more concerning the percentage strength of the reagent. At Johns Hopkins Hospital, he found that Dr. Wolman was not using full strength tuberculin, considering that it was likely to react in cases not clinically tuberculous.

He would ask Dr. C. von Pirquet if he had ever applied tuberculin to a blistered surface. In Leeds he (Dr. Woodcock) had been doing this during the last few months.

Two small blisters, one as a control, were made between the scapulæ. The blistered surfaces were treated with water dressing for twenty-four hours, then to one blister surface, one or two drops of tuberculin (either O. T. or T. R.) were applied. In another twenty-four hours' time the reaction showed itself, often with brilliant effect.

He advised that the von Pirquet reaction, or if the patient objected to what he associated with "vaccination," a blister reaction be tried always in preference to a Calmette.

Dr. von Pirquet at once replied that he had not used this blister method.

KUTANE UND KONJUNKTIVAL-TUBERKULINREACTION.

Von Dr. A. Wolff-Eisner,
Berlin.

Die neuen Tuberkulinreactionen haben in theoretischer und praktischer Beziehung einen weiten Ausblick eröffnet und die Diskussion über manche Frage, die zum Stillstand gekommen war, von neuem wieder angeregt. Ich betrachte es heute nicht als meine Aufgabe, alle die so wichtigen theoretischen Fragen ausführlich zu berühren, was auch wegen der notwendigen zeitlichen Beschränkung nicht ausführbar wäre; ich werde mir nur gelegentlich gestatten, auf die Stellen zu verweisen, an denen der Interessent die gewünschte Aufklärung findet. Ich glaube, es entspricht mehr den Aufgaben einer Sitzung, die so verschiedene Abteilungen vereint, einige praktische Fragen herauszugreifen und zu versuchen, sie einer gewissen Klärung zuzuführen.

Eine ganze Reihe neuer Reactionen für den klinischen Gebrauch sind uns in den Schoss gefallen; eine unübersehbare Literatur hat sich an die grundlegenden Veröffentlichungen angeschlossen. In der Mehrzahl war die diesbezügliche Literatur leider mehr extensiv als intensiv, und zeigte eine Nichtachtung dessen, was irgend ein anderer auf dem Gebiete publiziert hatte. Sie erlassen mir wohl die wenig erquickliche Aufgabe, hierfür Beispiele anzuführen. So ist es aber gekommen, dass die neuen Reactionen sich bisher als ein Dauergeschenk erwiesen haben, das mehr Verwirrung als Aufklärung gebracht hat und vorläufig ein Kampffeld darstellt, dem der praktische Arzt mit Recht aus dem Wege geht.

Die Zeit des Sturmes und Dranges wird vorübergehen; sie war eine notwendige Folge der kritiklosen Anpreisungen der Methode; die Warnungen des Referenten verhallten ungehört. Wir haben jetzt also die alte Koch'sche Subkutanreaction, die fast ebenso alte, aber erst jetzt aus langer Ruhe emporgehobene Stichreaction, die Kutanreaction und die Konjunktivalreaction nebst einer Reihe weiterer "neuer" Reactionsformen, auf die ich heute nicht weiter eingehen werde.

Die Subkutanreaction ist eine spezifische Methode, ein überaus feines Reagens auf Tuberkulose. Darum sind diejenigen im Rechte, die aus ihrem positiven Ausfall den Schluss auf vorhandene Tuberkulose ziehen, nicht aber

diejenigen, welche aus ihrem positiven Ausfall auf aktive oder klinische Tuberkulose schliessen. Davor sollten die positiven Ergebnisse der Subkutanprobe in 50 bis 80% bei klinisch Gesunden schützen. Ich würde nicht wagen, vor einem Forum, wie das hier versammelte, auf eine so selbstverständliche Sache einzugehen, wenn wir nicht tatsächlich gegen diese grundlegende Tatsache noch täglich in Praxis und Literatur Verstössen begegneten.

Die Kutan- und die Stichreaction stimmen im grossen und ganzen mit den Ergebnissen der Subkutanmethode befriedigend überein und damit ist ihre Rolle und ihre Bedeutung festgelegt: sie sind sehr bequeme und gefahrlose Methoden, welche die Subkutanreaction ersetzen und die gleichen Schlussfolgerungen gestatten wie diese: den Schluss auf eine vorhandene Tuberkulose, die aber inactiv latent sein kann.

Anders verhält sich die Konjunktivalreaction, die sich von der Stich- und Kutanreaction als Schleimhautreaction prinzipiell unterscheidet. Sie ist positiv bei aktiver Tuberkulose, soweit dieselbe nicht weit fortgeschritten ist und ist—von Ausnahmefällen abgesehen—bei klinisch Gesunden negativ. Schon heute hat es sich herausgestellt, dass ein Teil dieser anscheinend Gesunden mit positiver Konjunktivalreaction doch aktiv tuberkulös war; ob es mit den übrigen 5 bis 8% ebenso steht, wird die Zukunft erst zeigen können. Aber heute schon können wir sagen: im Gegensatz zu allen andern Tuberkulinreactionen ist die Konjunktivalreaction diejenige, welche auf das Vorhandensein einer aktiven Tuberkulose hinweist. Zeigt ein anscheinend Gesunder eine positive Konjunktivalreaction, ist er als dringend suspect auf das Vorhandensein aktiver Tuberkulose zu betrachten.

Dies beweisen die bisher vorliegenden Tatsachen, wenn man die Ergebnisse von 400 angestellten Reactionen auf das vorsichtigste bewertet. Der diagnostische Wert liegt in der positiven Reaction; es ist nirgendswo von mir ausgesprochen, dass etwa bei negativer Konjunktivalreaction das Vorhandensein einer aktiven Tuberkulose als ausgeschlossen zu betrachten sei; doch ist eine solche immerhin unwahrscheinlich, falls nicht eine klinisch manifeste Tuberkulose vorliegt.

Aus den mitgeteilten Gründen ist daher die Konjunktivalmethode der Subkutanreaction in diagnostischer Beziehung überlegen. Wir hatten sie anfangs nur für gleichwertig gehalten, sind aber durch vergleichende Untersuchungen an ca. 100 Fällen zu diesem Ergebnis gekommen.

Die prinzipielle Differenz der Tuberkulin-Lokalreactionen vor der Subkutanmethode beruht in der Erzeugung einer typischen Tuberkulinreaction fern vom etwa vorhandenen Krankheitsherde, also in der Vermeidung einer Herdreaction. Nicht die Temperatursteigerung bringt bei der Subkutantuberkulininjection die Gefahr mit sich, sondern die stets unberechenbare Herdreaction. In der Erkennung dieses prinzipiellen

Vorzuges sind auch gleich die Kontraindicationen enthalten, die ich von Anfang an eingehalten und nur einmal in Folge eines Versehens vernachlässigt habe. Noch bevor traurige Erfahrungen die Richtigkeit meiner theoretischen Voraussetzung erwiesen, hatte ich Mitte Dezember, 1907, in der ophthalmologischen Gesellschaft zu Berlin die (gleichen) Kontraindikationen mitgeteilt.

Sie beruhen in der Vermeidung von Herdreaktionen. Die Konjunktivalreaction ist also vor allem kontraindiziert wenn am Auge tuberkulöse Affectionen bestehen, bestanden haben oder vermutet werden; ferner in der Vermeidung von Wiederholungsreactionen am selben Auge, die ebenfalls Herdreactionen sind und dazu diagnostisch wertlos sind, weil sie nur den gleichen diagnostischen Schluss zulassen wie eine Kutanreaction, nämlich den auf eine vorhandene Tuberkulose, die latent sein kann. Ferner in Verwendung zu konzentrierter Präparate, vor allem der sogenannten Testpräparate, deren Schädlichkeit besonders dann in Erscheinung tritt, wenn, wie es vorkommt, es übersehen worden ist, dass die Konjunktivalreaction in dem betreffenden Fall als Herdreaction eigentlich kontraindiziert gewesen wäre.

Ich empfehle zur Konjunktivalreaction das von mir auf Wirksamkeit und Unschädlichkeit geprüfte "Tuberkulin zur Ophthalmoreaction Ructe-Enoch" in 1 bis 2% Lösung. Mit höheren Conzentrationen lassen sich wohl bessere Statistiken erzielen, d. h. es lassen sich bei aktiv tuberkulösen in noch höheren Prozentzahlen positive Reactionen hervorrufen, aber ich lege auf eine solche Paradestatistik keinen Wert, denn die auf diese Weise erzwungenen Reactionen betreffen Fälle, bei denen die klinische und die Sputumuntersuchung sowieso an der Diagnose keinen Zweifel lässt; bei den initialen Fällen giebt die nach meinen Grundsätzen angestellte Reaction so deutliche Aufschlüsse, dass kein Grund besteht, von der absolut gefahrlosen Form der Reactionsanstellung abzugehen. Zudem würde man sich des prognostischen Anhaltes begeben, den der negative Ausfall der Konjunktivalreaction bei manifest Tuberkulösen gerade bei Benutzung einer so abgestimmten Lösung, wie ich sie verwende, gewährt.

Wenn ich mich nun den einzelnen Sectionen zuwende, welche das Interesse an der Konjunktivalreaction hier zusammengeführt hat, so erkenne ich unumwunden an, dass die Ophthalmologen die kompetenten Beurteiler der Konjunktivalreaction sind, nur müssen auch sie die Kontraindicationen beachten und ihre Erfahrungen an internem Material machen. Leider haben die Ophthalmologen fast durchweg die Kontraindicationen in keiner Weise beachtet und sind so die Ursache geworden, dass die Konjunktivalreaction sich erst sehr mühsam durch Vorurteile infolge von Publikationen von Ophthalmologen einen Weg bahnen muss.* Es ist wohl kein Zufall,

* Wiener klin. Woch., 1908, No. 33.

dass die Sile'sche Klinik, die meine Vorschriften aufs genaueste beachtet hat, sehr günstige Erfahrungen mit der Konjunktivalmethode gemacht hat (Erlanger).

Ueber die diagnostische Verwertbarkeit der Konjunktivalreaction in der internen Medizin haben wir schon gesprochen. Nur hört man bisweilen, die Reaction ist ganz unzuverlässig, sie ist bei Tuberkulösen negativ und bei klinisch Gesunden positiv. Meine Herren! wer dies sagt, sagt nur dasselbe, was ich schon mitgeteilt habe, aber die Form lässt erkennen, dass der Betreffende kein guter Kliniker sein kann. Er vergisst mitzuteilen, dass die negativen Reactionen sich bei manifest Tuberkulösen finden und dass die "Gesunden" nach dem Ausfall der Konjunktivalreaction als viel suspecter (4–10 mal) anzusehen sind, als nach einer positiven Subkutanreaction, der viele Kliniker doch noch eine grosse Bedeutung zuerkennen.

Auch über die prognostische Bedeutung der Konjunktivalreaction sind vielfach irrtümliche Anschauungen verzeichnet. Trotzdem kann ich konstatieren, dass diese von Anfang an lebhaft verkündete Anschauung langsam, aber sicher an Terrain gewinnt. Darum liegt mir daran, offenbare Irrtümer in der Literatur richtig zu stellen. Ich habe der negativen Konjunktivalreaction nur bei manifester Tuberkulose (positiver Bazillenbefund) eine ungünstige prognostische Bedeutung zugesprochen, aber nie gesagt, dass aus der positiven eine günstige Prognose zu erschliessen sei und weiter niemals behauptet, dass eine negative Konjunktivalreaction bei positiver Subkutanreaction eine ungünstige Prognose bedinge. Da ich in so gelagerten Fällen eher auf eine latente Tuberkulose schliesse, tue ich so in Wirklichkeit das umgekehrte, als was Röpke* mir imputiert. Die andern von Teichmann und mir gezogenen prognostischen Schlussfolgerungen† beziehen sich sämtlich auf den Ablauf der Kutanreaction. Ich möchte ausdrücklich die s. Zt. gezogenen prognostischen Schlussfolgerungen, denen ich mit Recht von Anfang an eine mindestens ebenso grosse Bedeutung wie den diagnostischen gegeben habe, in allen wesentlichen Punkten aufrecht erhalten, weil sie sich im weiteren Verlauf der Beobachtungen durchaus bestätigt haben. Es ist diese Prognosenstellung einer von den Gründen, die mich veranlassen, stets zusammen mit der Konjunktivalreaction auch die Kutanreaction anzustellen.

Es hat die Prognosenstellung aus dem Ablauf der Reaction durchaus nichts so Mystisches, wie es manchem wohl scheint. Man nehme eine kutane Dauerreaction, die nach meinen Ausführungen Ausheilung oder günstigen Verlauf kennzeichnet. Diese Dauerreaction ist ein Zeichen, dass an der Reactionsstelle der Körper auf die Einverleibung von Tuberkelbazillengiften mit Bindegewebsbildung reagiert. Man braucht nur anzunehmen, dass im

* Brauers Beit., Bd. ix, H. 3.
† Berl. klin. Woch., 1908, No. 2.

Krankheitsherd der Körper auf die gleichen Gifte ebenso reagiert oder reagiert hat, und der aus der Dauerreaction gezogene Schluss auf Ausheilung oder günstige Prognose hat nichts Mystisches mehr; es wird dann niemand mehr wundern, dass die empirische Beobachtung der Tatsache zu dem gleichen prognostischen Schluss geführt hat.

Es herrscht hier eine strenge Logik der Tatsachen, deren Zusammenhang oft im ersten Augenblick nicht offenbar wird. Ich habe gemeinsam mit Wolfsohn eine grosse Anzahl von Opsoninuntersuchungen ausgeführt und wir sind zu dem Schluss gekommen, dass die mühsame Technik in diagnostischer Beziehung meistens nicht mehr leistet, als die genaue klinische Beobachtung und die Anstellung der Lokalreaction. Etwas anders ist es in therapeutischer Beziehung mit der Kontrolle einer Tuberkulinkur durch Opsoninbestimmung.

Wir gingen von der Annahme aus, dass bei starken Tuberkulinreactionen, besonders aber bei den Dauerreactionen sich ein hoher Opsoningehalt finden würde. Es war dies absolut nicht der Fall und erst allmählich wurde klar, aus welchem Grund. Ein hoher Opsoningehalt kommt dadurch zu Stande, dass vom Herd aus Tuberkelbazillengifte resorbiert werden. Durch Bindegewebsbildung wird diese Resorption verhindert und das Fehlen hoher Opsoninwerte genügend erklärt.

Durch die Opsoninversuche, ebenso durch unsere Komplementbindungsversuche bei Tuberkulose* wird festgestellt, dass bei allen Tuberkulösen Tuberkelbazillengifte zur Resorption gelangen, die in ihrer Wirkung mit dem Tuberkulin übereinstimmen. Es ist diese Feststellung von der allergrössten prinzipiellen Bedeutung, weil sie die Erklärung abgiebt für die Angaben vieler Forscher, die bis heute sich unaufgeklärt gegenüberstanden. Es ist bekannt, dass heute noch Anhänger und Gegner der Tuberkulinanwendung der diagnostischen wie der therapeutischen vorhanden sind, dass die einen fortwährend über Schädigungen berichten, welche den andern nie zur Beobachtung gekommen sind.

Die obige Feststellung erklärt, dass bei einer Tuberkulininjection dem Patienten nichts passiert, was ihm nicht event. durch vom Herd resorbiertes Tuberkulin auch im Verlaufe seiner Krankheit geschehen könnte. So ist es vollkommen dem Temperament eines jeden überlassen, was er auf den Krankheitsverlauf, was er auf eine Tuberkulinschädigung zurückführen will. Und das Temperament wird beeinflusst durch eine dogmatische Stellungnahme als Tuberkulinfreund oder Gegner, denn diejenigen, welche unparteiisch diese Fragen prüfen, sind noch heute spärlich gezählt.

Die gleiche Feststellung erklärt auch die geradezu paradoxe Tatsache, dass die Statistik der Tuberkulinfreunde und Gegner gar nicht so besonders von einander abweicht; ich sehe hier davon ab, dass der Statistik bei Lungen-

* Wien. klin. Woch., 1908, No. 37.

krankheiten noch überhaupt eine Basis fehlt, worüber ich an anderer Stelle sprechen werde.

Wenn aber bei jedem Tuberkulösen Tuberkulin in den Kreislauf gelangt, so ist es verständlich, wenn die Erfolge bei mit und ohne Tuberkulininjection behandelten Kranken gar nicht so prinzipiell verschieden ausfallen. Es wird sich in Zukunft darum handeln, individualisierend diejenigen herauszufinden, welche Tuberkulinzufuhr nötig haben. Die Beobachtung der Lokalreaction, der Opsonine und des klinischen Verlaufs giebt hier Anhaltspunkte.

Zahlreiche Versuche, die Beobachtungen der Lokalreactionen und Versuche anderer Forscher haben mich zu der Ueberzeugung gebracht, dass es eine gewisse Immunität bei Tuberkulose giebt und zwar eine gegen die Tuberkelbazillen gerichtete und eine gegen die resorbierbar gewordenen Giftstoffe. Sie ist mit grösster Wahrscheinlichkeit eine bakteriolytische; die gegen die durch Lyse frei gewordenen Giftstoffe gerichtete ist keine antitoxische, sondern entspricht dem kürzlich von mir klar gelegten Mechanismus der natürlichen Immunität gegen Toxine durch Bindung an Organreceptoren, die gegenüber Endotoxinen häufig am Bindegewebe sitzen im Gegensatz zur aktiven Toxinimmunität des empfänglichen Tieres.* Zwei Fälle mögen dies illustrieren: an beiden war die Kutanreaction angestellt; sie erhielten 1, 3, 5 mg. Tuberkulin subkutan und reagieren mit steigendem Fieber; bei 7 und 9 mg. bleibt die Allgemeinreaction aus, an Stelle dessen ein kolossales Aufflammen der alten Kutanreaction. (1 x wie ein Erysipel, 1 x wie ein riesiges Furunkel.)

Solche Beobachtungen, die beim Rind ganz konstant von mir erhoben wurden, kann man alle Tage machen; ihre Deutung bereitete jedoch grosse Schwierigkeiten und ist nur für den möglich, der sich experimentell bei den einfacher liegenden Verhältnissen bei der natürlichen Toxinimmunität eine Vorstellung gebildet hat.

Das (wahrscheinlich durch lytische Prozesse resorbierbar gewordene) Tuberkulin geht an die Stellen, welche Receptoren besitzen; es sind dies zunächst die Krankheitsherde, es lassen sich aber auch an andern Orten solche als Herde fungierende Stellen mit Receptoren schaffen. Wird hier alles Tuberkulin gefunden, so kommt es bei Injection von Tuberkulin nur zu Lokalreactionen; wird es partiell oder nur zeitweise gefunden, so kommt es zu abgeschwächten oder verspäteten Herd- und Allgemeinreactionen.†

Wir sind so in der Lage, durch Verlegen der Giftwirkung an Stellen von relativ geringer vitaler Bedeutung, z. B. ins Bindegewebe, den Organismus

* Zentrbl. f. Bakt., 1908.

† 1. So erklärt es sich, dass nach Tuberkulininjection die Lokalreactionen vor der Allgemeinreaction aufflammen können, event. auch ohne dass die erwartete Allgemeinreaction nachfolgt. (Cf. Die Ophthalmodiagnose, Wolff-Eisner, Würzburg, 1908.)

von der Giftwirkung der Tuberkelbacillen freizuhalten; wir werden wohl auch lernen, diese Feststellung therapeutisch zu verwenden.

Ausgehend von der Erwägung, dass die Schaffung solcher Receptoren im Bindegewebe am zweckmässigsten sein würde und weiter von der von Holländer und Joseph u. a. vielfach gemachten Beobachtung, dass gewisse Formen der Hauttuberkulose Tuberkulose der Lunge, etc., oft ausschliesst oder ihren Verlauf günstig beeinflusst, erzeuge ich seit einiger Zeit bei lungenkranken Patienten künstlich Hautherde durch intrakutane Injection kleiner Tuberkulindosen und durch Einreibung von Tuberkulinsalbe. Ich werde demnächst in der zweiten Auflage meiner Ophthalmodiagnose über die Grundlagen dieser Therapie ausführlicher berichten, werde mich aber trotz vorliegender günstiger Erfahrungen nicht verleiten lassen, vorzeitig über Erfolge zu berichten.

So hängt auf diesem Gebiete das rein theoretische mit praktischen Erfolgen auf das engste zusammen, wofür die Konjunktivalreaction selbst, der Ausgangspunkt unserer Betrachtungen, der sprechendste Beleg ist.

Den hier anwesenden Veterinär-Medicinern möchte ich mitteilen, dass die Uebertragung der Konjunctivalmethode auf das Rindvieh ausserordentliche Schwierigkeiten bot. Bei Versuchen, die ich im Auftrag und mit Unterstützung des Landwirtschaftsministeriums ausführte, ist es gelungen, die Hauptschwierigkeiten zu überwinden. Es ist zu hoffen, dass auch für die Veterinärpraxis die Konjunktivalreaction sich zu einer ebenso exacten Methode wird ausbilden lassen, wie beim Menschen.

Ich fasse meine Ausführungen kurz zusammen.

1. Die Subkutan- und Kutan-Methode ist eine specifische Reaction auf Tuberkulose; da beide auch latente Tuberkulosen anzeigen, sind sie für die klinische Diagnostik nur mit grösster Einschränkung verwendbar.

2. Die positive Konjunktivalreaction zeigt aktive Tuberkulose an.

3. Ihr Auftreten bei klinisch Gesunden macht diese dringend suspect.

4. Ihr negativer Ausfall bei manifester Tuberkulose hat eine prognostisch ungünstige Bedeutung.

5. Die negativen Reactionen werden mit dem Fortschreiten der tuberkulösen Erkrankung immer häufiger.

6. Aus einer positiven Konjunktivalreaction ist kein Schluss auf eine günstige Prognose zu ziehen, sondern nur aus der sogenannten kutanen Dauerreaction.

7. Es ist möglich, in für das Leben indifferenten Gewebsteilen, wie z. B. das Bindegewebe, Receptoren zu schaffen, welche Tuberkulin an sich ziehen und die Giftwirkung lokalisieren. Es lässt sich diese Beobachtung therapeutisch verwenden.

El Diagnostico Prematuro de la Tuberculosis.—(WOLFF-EISNER.)

Percusion del vertice del pulmon, por el metodo de Krönig, es el metodo clinico mas importante. Un por ciento crecido de linfocitos en la exudacion indica la citologia tuberculosa (Widal, A. Wolff). Los linfocitos en el esputo son un signo importante del principio de la afeccion tuberculosa; estos son aparentes antes que el bacilo. La inyeccion subcutanea de la tuberculina es una prueba muy delicada de la existencia de la tuberculosis; mas como esta tambien demuestra la tuberculosis latente, su valor clinico es relativamente ligero. Lo mismo puede decirse de la reaccion cutanea, la cual puede, sinembargo, emplearse en el diagnostico por el hecho de que esta difiere de la inyeccion subcutanea en que es sin peligro, y por que un resultado negativo es de un valor considerable. La reaccion de la conjuntiva da un resultado positivo solamente en la presencia de la tuberculosis activa. Se puede probar que la reaccion es positiva en 85% de los casos de tuberculosis en el periodo iniciativo, y conversamente, solamente un 25% de los individuos en una salud aparente dan una reaccion positiva, en comparacion con el metodo subcutaneo. En un numero de personas aparentemente sanas, la existencia de una tuberculosis activa fue mas tarde demostrada. La reaccion de la conjuntiva es absolutamente sin peligro cuando se observan las contraindicaciones. En vez de la llamada preparacion de la prueba, que no debe ser recomendada, la prueba debera hacerse con la tuberculina de Ruete-Enoch, Hamburgo, que es probada y esta bajo mi direccion. La instilacion secundaria debera evitarse, puesto que esta no tiene valor en el diagnostico, y aunque una reaccion se presente, esto no indica de que hay una tuberculosis activa; por lo tanto esto no da ninguna indicacion que no sea obtenida por medio de una reaccion cutanea. La prueba de la tuberculina en la conjuntiva no deberá hacerse con el uno por ciento de la tuberculina cuando exista una tuberculosis activa del ojo, o cuando el paciente haya tenido un ataque de queratitis tuberculosa, o conjuntivitis flictenular. A medida que el proceso tuberculoso avanza, el numero de la reacciones locales positivas constantemente disminuyen. Hay casos, siembargo, que faltan á la reaccion aun en el periodo inicial. Se ha demostrado que una falta de la reaccion cutanea y de la conjuntiva, es un signo diagnostico desfavorable cuando existe una tuberculosis activa con la presencia del bacilo de la tuberculosis; mas no bajo otras condiciones. Otros datos del pronostico deberan obtenerse por la reaccion cutanea en la forma curativa. Yo distingo la reaccion normal que corre su curso en cuatro dias; la reaccion rapida, que termina en veinte y cuatro horas, y que indica un pronostico desfavorable; la reaccion permanente, que persiste por espacio de seis a veinte dias, y que es un signo favorable en el pronostico; este es observado principalmente en los casos curados de la tuberculosis. La significacion del

pronostico de la reaccion es muy important. Los datos teoreticos que se han obtenido directa o indirectamente, por medio de la reaccion local, han sido de gran valor en la investigacion de la tuberculosis. Ellas no seran mencionadas sino a la ligera, sinembargo, con referencia a mi memoria publicada por Stuber, Wurzburg, en 1908, titulada, "Die Ophthalmo- und Cutandiagnose der Tuberkulose"; y la segunda edicion de la misma que sera publicada al fin del presente año. Una translacion inglesa fue traida de Londres por John Bale, Sons, y Danielson, Limited, Londres, 1908. La reaccion de la conjuntiva fue comunicada por Wolff-Eisner el 15 de Mayo de 1907, a la Berlin. med. Gesellschaft. Le segunda comunicacion sobre el tema aparece el 16 de Junio de 1907, en la academia de Paris, simultaneamente por Calmette y Vallee. Los esfuersos de Calmette han contribuido conciderablemente al empleo de esta reaccion en la clinica. Muchas interpretaciones erroneas se encuentran en la Literatura Inglesa y Americana.

The Early Diagnosis of Tuberculosis.—(WOLFF-EISNER.)

Percussion of the apices, after Körnig, is the most valuable clinical method. A high percentage of lymphocytes in an exudate points to a tuberculous etiology (Widal, A. Wolff). Lymphocytes in the sputum are an important early symptom of beginning tuberculosis; they make their appearance before the tubercle bacilli.

The subcutaneous injection of tuberculin is a very delicate test of the existence of tuberculosis; but as it also shows latent tuberculosis, its clinical value is relatively slight. The same is true of the cutaneous reaction, which may, however, be employed for purposes of diagnosis because it differs from the subcutaneous injection by being absolutely free from danger, and because a negative result is of considerable diagnostic value.

The conjunctival reaction gives positive results only in the presence of active tuberculosis. It can be proved that the reaction is positive in 85 per cent. of all cases of active tuberculosis in the initial stage, and, conversely, only 25 per cent. of apparently healthy individuals react positively as compared with the subcutaneous method. In a number of apparently healthy persons the existence of active tuberculosis was later demonstrated.

The conjunctival reaction is absolutely without danger if the contra-indications are observed. Instead of the so-called test-preparations, which are not to be recommended, the test should be made with tuberculin Ruete—Enoch, Hamburg—which is tested and is under my control. Secondary instillations should be avoided, for they have absolutely no diagnostic value, since, even if a reaction occurs, it does not prove that there is active tuberculosis; hence it affords no more information than is obtained

from a cutaneous reaction. The conjunctival test with 1 per cent. tuberculin should not be employed when there is actual or suspected ocular tuberculosis, and when the patient has had an attack of tuberculous keratitis or phlyctenular conjunctivitis.

As the tuberculous process advances, the number of positive local reactions constantly diminishes. There are cases, however, which fail to react even in the initial stage. It has been shown that failure of the cutaneous and conjunctival reactions is an unfavorable diagnostic sign when there is manifest active tuberculosis with tubercle bacilli; but not under any other circumstances.

Further prognostic data may be obtained by plotting cutaneous reaction in the form of a curve. I distinguish the normal reaction, which runs its course in four days; the rapid reaction, which is complete in twenty-four hours and indicates an unfavorable prognosis; the permanent reaction, which persists for from six to twenty days, and is a favorable prognostic sign; it is observed chiefly in cases of healed tuberculosis.

The prognostic significance of the reactions is very great.

The theoretical data which have been obtained either directly or indirectly by means of the local reactions have been of the greatest value in the investigations on tuberculosis; they will be passed over, however, with a reference to my monograph, published by Stuber, Würzburg, in 1908, entitled, "Die Ophthalmo- und Cutan-diagnose der Tuberkulose"; and the second edition of which will appear at the end of the present year. An English translation was brought out in London by John Bale, Sons, and Danielson, Limited, London, 1908.

The conjunctival reaction was reported by Wolff-Eisner on the 15th of May, 1907, to the Berliner med. Gesellschaft. The next communication on the subject appeared on the 16th of June, 1907, in the Paris académie, simultaneously by Calmette and Vallée. Calmette, by his efforts, greatly contributed to the introduction of the reaction into clinical medicine. Many erroneous statements are found in the English and American literature.

CONCLUSIONS FROM 1087 CONJUNCTIVAL TUBERCULIN TESTS BY A UNIFORM METHOD.

By Edward R. Baldwin, M.D.,
Saranac Laboratory, Saranac Lake, N. Y.

The reports which form the basis of this contribution were obtained from forty physicians engaged in tuberculosis work, most of whom are clinicians, and to whom my acknowledgments are herewith made with thanks. The same preparation of tuberculin was furnished to all, together with an eye-dropper graduated to 0.25 c.c. The material was obtained from 500 c.c. of old tuberculin (human), precipitated with alcohol and redissolved in normal salt solution when sent out from the laboratory. It had been filtered through a thick Berkefeld bougie, and contained no dead tubercle bacilli or fragments recognizable by staining. Some preliminary tests by the author made it appear that the percentage used by Calmette (1 per cent.) was dangerously strong, at least for this preparation. Hence the solutions were made $\frac{1}{3}$ per cent., and $\frac{1}{2}$ per cent. in sterilized sealed tubes, and provisional directions given to begin with the weaker and repeat in the other eye with the stronger if no reaction occurred to the first instillation. Contraindications to the employment of the test were also suggested where any eye disease existed, as these seemed more or less obvious. To the use of a small measured drop, weak sterile solutions and the observance of contraindications may be attributed in part the rarity of severe or prolonged reactions and sequelæ. But one instance of keratitis has been reported, and that in a scrofulous subject.* The reports herein contained do not comprise all† the tests made with the same preparation of tuberculin, but a request made to those clinicians who were unable to report their tests in detail for a report of any injurious effects noted has not produced any further cases. Six hundred additional tests were cited without resulting injury, 100 being on infants.

Practically all the tests were made within three months of the date when the solutions were prepared, and no deterioration in strength was

* Completely recovered without opacity.

† They include the cases published by Drs. C. Floyd and J. B. Hawes, 2d (Journal Med. Research, 1908, No. 4, vol. xvii), and also most of those reported by the writer in the Journal (Chicago), December 14, 1907, vol. xlix.

noted except in some tubes kept six months. It is, however, probable that some reactions failed to appear from this cause.

In the following tables are presented the results as collated from record charts sent to all the recipients of the tuberculin. They include 887 individuals, in 190 of whom a second instillation was made in the opposite eye, and 10 in the same eye—a total of 1087 instillations.*

There were 310 cases of tuberculosis in some form, 265 suspected tuberculous, 127 subjects of other diseases, and 185 supposedly healthy subjects. Doubtful reactions are excluded from the tables.

TABLE I.—SUMMARY.

		Cases.	Reacted Positively.	Per Cent.		Cases.	Reacted Positively.	Per Cent.
Pulmonary Tuberculosis	Stage I (Incipient): Tubercle bacilli demonstrated	33†	20	60	Suspected tuberculosis, pulmonary	219	73	33.3
	Tubercle bacilli not demonstrated	49	35	71.4	Other forms.	46	22	47.8
		82	55	67.0	..	265	95	35.9
	Stage II (Moderately advanced): Tubercle bacilli demonstrated	96 ‡	76	79.2	Other diseases.	127	19	14.1
	Tubercle bacilli not demonstrated	22 §	13	59.1	Healthy (unsuspected)	185	34	18.3
		118	89	75.0				
	Stage III (Far advanced)	36	18	50.0				
	Clin. healed	24	17	70.0				
	Other forms of tuberculosis	50‖	39	78.0				
	Total	310	218	70.0				

In reviewing the percentages in Table I, it is apparent that a considerably greater number of pulmonary cases reacted in the moderately advanced class than in the incipient, while in the far advanced the number was less. It is

* A few received a third instillation with another tuberculin.
† Nine were under tuberculin treatment and failed to react.
‡ Nineteen were under tuberculin treatment, of whom 10 reacted positively.
§ One was under tuberculin treatment and failed to react.
‖ Eight were under tuberculin treatment, of whom one reacted.

probable that the patients forming the moderately advanced class, being taken from sanatoriums, in the greater part were in better condition than the hospital cases tested by Wolff-Eisner, who found a decreased percentage of reactions with the advance of the disease. The influence of tuberculin treatment in lowering the sensitiveness of the conjunctiva brought down the percentage of reactions appreciably. It is also noteworthy that fully 70 per cent. of persons healed in the clinical sense from two to thirty years, reacted positively. The chief interest relates to the clinically incipient (71.4 per cent., positive) and suspected cases (33.3 per cent. positive), where the test would be expected to assist in diagnosis. The results fall considerably short of the requirements for an ideal diagnostic method in suspected tuberculosis, though relatively good in confirmation of the clinically tuberculous cases. The percentage of supposedly healthy and non-tuberculous diseases reacting positively closely accords with that found by Wolff-Eisner and Petit in a larger number of cases.

Age Divisions.

Table II shows the age divisions and positive reactions. From this it will be seen that 15.2 per cent. were children under fifteen years of age. The number of patients in the youngest and oldest classes is too small to attach any importance to the percentage of reactions. The high percentage of positive results in the age division 10 to 15 is noteworthy, especially in the non-tuberculous diseases, when compared with the older classes. Probably no significance can be properly given to such small numbers of cases.

TABLE II.—AGE DIVISIONS.

	Ages 0–10.	React. +.	Per Cent.	Ages 10–15.	React. +.	Per cent.	Ages 15–40.	React. +.	Per Cent.	Ages 40 up.	React. +.	Per Cent.	Total React. +.	Per Cent.
Tuberculosis:														
All forms.....	20	8	40.0	26	24	92.3	238	162	68.0	39	24	61.6	218	70.0
Suspected.....	5	1	20.0	45	21	46.6	193	69	35.7	22	4	18.1	95	35.9
Other diseases .	16	5	31.2	16	7	43.7	73	3	4.1	22	4	18.1	19	14.1
Healthy.....	3	0	0.0	4	0	0.0	157	27	17.0	21	7	33.3	34	18.3
Total.....	44			91			661			104				

A history of tuberculosis in the family or of exposure to the disease was not fully reported, but in 62 suspected cases with family tuberculosis 50 per cent. reacted; of 35 healthy persons with like history, 25.7 per cent. reacted.

Severity of Reactions.

The grade of reaction severity was not recorded as fully as desired, although the scheme in Table III was originally suggested for this purpose to the recipients of the tuberculin. The following meaning is to be understood from the signs:

\+ Distinct palpebral redness with secretion.

\+ + Ocular and palpebral redness with secretion.

\+ + + Deep injection of entire conjunctiva with edema of lids, photophobia, and secretion.

TABLE III.—SEVERITY OF REACTIONS.

	+	++	+++	Prolonged Conjunctivitis.	Sequelæ.
Pulmonary tuberculosis I — Tubercle bacilli demonstrated	9	11	3	..	..
Pulmonary tuberculosis I — Clinical	16	13	3	..	..
Pulmonary tuberculosis II — Tubercle bacilli demonstrated	50	22	4	5— 5 days.	..
Pulmonary tuberculosis II — Clinical	11	1	1		..
Pulmonary tuberculosis III	12	4	2	1— 8 days.	..
Clinically healed	14	5	1	1—10 days.	..
Other forms of tuberculosis	11	22	6	1—12 days. 2— 7 days.	1 keratitis (scrofula, æt 22)
Pulmonary tuberculosis suspected	48	14	1	..	..
Other forms of tuberculosis suspected	22	?	?	..	..
Other diseases	13	6	?	..	..
Healthy (unsuspected)	19	8	3	..	..
Total	225	106	24	10	1

Comment may be made on the fact that severe reactions were not confined to the well-marked tuberculous subjects, but occasionally were produced in apparently healthy persons. The strongest reactions, however, were more frequent in the first stages of tuberculosis. The small number (24) of very severe and (10) prolonged reactions has already been noted. Three severe reactions were accompanied by coryza in the corresponding nostril and constitutional symptoms—slight fever, malaise, and muscular pains; one of these had a nosebleed.

Repetition of the test in the same eye was recorded in 10 cases, and in the opposite eye in 190, who had not reacted to the first test. All the first were tuberculous or suspected, so that little value can be placed on the reactions (which occurred in all) as indicative of acquired sensitiveness in hitherto uninfected subjects. The reactions to repetition in the same eye

were nevertheless severe, as shown in the following table, and illustrate the heightened sensitiveness produced by the first instillation. The interval between the first and second instillations in the same eye was from two weeks to two months, which was sufficient for the creation of antisubstances.

TABLE IV.

		No.	+	++	+++	Per Cent.
Second instillation	Same eye	10	1	2	7	100
	Opposite eye	190	29	7	0	18

Only 18 per cent. of the opposite eyes responded positively, nearly all of which were in suspected or tuberculous subjects, and instilled within a week after the first test. The value of this method in increasing the percentage of reactions would seem to be relatively small.

Influence of Fever.

The presence of fever was reported in 67 tuberculous and 25 suspected cases. Where the degree was noted, only those of 99.5° F. and over are included (in the following table). Mouth temperatures are to be understood.

TABLE V.

		Cases.	React.
Pulmonary tuberculosis	Stage I:		
	Tubercle bacilli demonstrated	10	8
	Clin	10	6
	Stage II:		
	Tubercle bacilli demonstrated	22	21
	Clin	1	0
	Stage III:	17	9
	Other forms	7	7
	Suspected	25	8

It is apparent that the presence of fever does not diminish the chance of reaction, for even in the stage III cases, where the highest fever prevailed, the percentage is the same as in Table I for the whole number. The same may be noted in the suspected class where the subcutaneous test could not be employed in the presence of fever. On the other hand, the I. and II. stage tuberculous show a higher percentage.

Combined Conjunctival, Cutaneous, and Subcutaneous Tests.

The next table shows the results in the cases subjected to control tests. The cutaneous tests were usually made subsequent to the conjunctival, and all the subcutaneous tests were thus made.

TABLE VI.

	Conjunctival.*	+	Cutaneous.	+	Subcutaneous.	+
Tuberculous	23	11	23	13	..	..
	31	13	..	..	31	18
Suspected	20	4	20	10	..	..
	35	7	..	..	35	18
Other diseases	2	1	2	0	..	..
	9	1	..	..	9	1
Healthy	7	1	7	4	..	..
	14	0	..	..	14	3
Total	141	38	52	27	89	40

In addition, 4 tuberculous cases were tested by the percutaneous method of Moro, with positive results in all.

Without mention of details as to maximum doses a full discussion of these tests is unprofitable. In many cases the reports were incomplete, but it is sufficient to note a fair correspondence between the reactions among the tuberculous and the larger proportion of reactions to the cutaneous and subcutaneous tests among the suspected and healthy. So far as they go these cases confirm previous observations of the relative reacting power of the tests, but no data of value were brought forward as to the prognostic value of the conjunctival reaction. Among the tuberculous patients tested by the writer no such regular correspondence between the degree of the reactions and the clinical prognosis was observed as was found by Wolff-Eisner and Stadelmann, except in the far-advanced class. Among 90 patients of all stages recorded as favorable, only 67 reacted; of 11 doubtful, 9 reacted, and of 35 unfavorable, 29 reacted strongly positive in most cases.

The future history alone can show whether the conjunctival reactions among the apparently healthy subjects betokened a state of greater danger of the outbreak of active tuberculosis in them than in the non-reacting individuals. It is too much to claim from these experiments that only those healthy persons reacted in the eye who had a more dangerous infection.

The conceivable causes of non-reaction to the conjunctival test must be regarded in estimating its diagnostic as well as its prognostic accuracy, and the value of such a standard is impaired for the following reasons: (*a*) Uncertain absorption of the tuberculin due to lacrimation and spasm of the eyelids, which may squeeze out the drop. (*b*) Smallness of the dose required for safety, it being insufficient to react all the first stage known

* The conjunctival reaction appeared for the first time in 4 cases during the subcutaneous reaction, and recurred in 2 cases at this time. Three of the first mentioned were suspected and the others clinically tuberculous.

tuberculous individuals. (*c*) Variations in individuals as to local sensitization acquired from tuberculous infections of equal amount.

By repeated instillations in the same eye, as practised by Roepke and others with increasing doses, no doubt a majority of all infected individuals would react as with the subcutaneous test.

Apart from the danger to the eye, it is by no means proved that uninfected individuals cannot be sensitized in this way, even if but slightly.

This naturally leads to the consideration of the value of any tuberculin reaction. The wide use of the conjunctival and skin tests during the past year has impressed many clinicians for the first time with their limitations. A positive reaction cannot be interpreted as an infallible criterion of existing disease. It only betrays the presence of the infection—whether recent or long healed is to be determined by other means. In reality reactions which take place only to large or repeated doses are of little clinical value considered apart from other symptoms. The absence of reaction after such methods is of far greater value in excluding tuberculosis. In a general way, no doubt, the more marked and prompt the reaction and the smaller the dose, the greater is the probability of the presence of an active or recent infection. In this way the conjunctival test may help, but it is possible that with suitable dilutions of tuberculin the cutaneous test will be found to have the same value for adults as for children. There will then be no advantage in the use of either the conjunctival or subcutaneous method, except when it is desired to produce a focal reaction at the site of disease when the latter would be required. It follows from these reflections that only positive reactions to very small amounts of tuberculin have much diagnostic importance in the presence of disease symptoms except where focal reactions can be observed, while only absence of reaction to repeated and large doses has any value in excluding tuberculosis.

Danger of the Conjunctival Reaction.

The reports from physicians who have employed the method and observed the precautions at first promulgated do not speak of the great risk to the eyes, yet the fact that harm can be done is undeniable, and should banish the promiscuous use of the conjunctival test in the opinion of the writer. When governed strictly by the indications as to the absence of past or present eye disease or scrofulous history, and the use of weak solutions not repeated, the risk is very slight; but as a few cases of corneal injury in alleged healthy eyes have been elsewhere reported, no one should employ the test without a feeling of responsibility. As compared with the subcutaneous test, any injurious results that may follow are less easily ascribed to coincidences, even if justly so.

Conclusions.

1. The conjunctival tuberculin test performed with weak solutions by a single instillation has some value in confirming the presence of tuberculosis in the early stages.

2. It has little value in confirmation when the symptoms of tuberculosis are only suspicious.

3. Its value in distinguishing "active latent" from healed tuberculosis in apparently healthy persons has not yet been determined.

4. Repetition of the test in the same eye has no advantage over the cutaneous and subcutaneous tests in the percentage of reactions produced, and may be misleading and dangerous.

5. Repetition in the other eye by the author's method offers so little advantage that it cannot be recommended.

6. The conjunctival reaction is unreliable for prognosis.

7. Used with the proper precautions, danger to the eye is slight, and need not preclude the test when other methods are inapplicable, as, for example, when fever is present. It should be restricted to adults, since the cutaneous test has been found equally valuable for children and is harmless.

8. The cutaneous test by the simultaneous use of dilute and strong tuberculin offers a method of detecting at once or excluding tuberculous infection with no danger or inconvenience. Further experience is needed to show the value of this method.

9. The subcutaneous test should be restricted to those cases where a reaction at the site of disease is desired, or where the other tests result negatively.

BIBLIOGRAPHY.

Wolff-Eisner (A.): Die Ophthalmo- und Kutan-Diagnose der Tuberkulose, etc., Würzburg, 1908.

Petit (Leon): Le diagnostic de la tuberculose par l'ophtalmo-reaction, Paris, 1907.

Roepke (O.): "Die Ergebnisse gleichzeitig angestellter Tuberkulin-reaktionen, etc.," Beit. zur Klin. der Tuberk., 1908, Bd. Ix, No. 3.

Conclusiones Deducidas de 1087 Pruebas de Tuberculina en la Conjuntiva, por un Método Uniforme.—(Baldwin.)

El autor ha recogido informes de cuarenta clinicos y médicos de Sanatorios á quienes se envió la misma tuberculina con las direcciones para seguir un método uniforme de prueba y para anotar los resultados. Fueron distribuidas dos soluciones de $\frac{1}{3}\%$ y $\frac{1}{2}\%$, respectivamente de tuberculina vieja purificada y seca, acompañadas de un gotero graduado á 0.25 c.c. Se indicaron contra-indicaciones para las pruebas en que se presentase alguna enfermedad en los los ojos. En el caso de que la solución más debil fallas, sea consejó repetir sólo en el ojo opuesto con la solución de $\frac{1}{2}\%$.

Nos informes comprenden 887 individuos, en 190 de los cuales se usó una segunda instilación en el ojo opuesto, y 10 en el mismo ojo. Hubo 310 casos de tuberculosis en alguna forma incluidos 24 casos de cicatrización pulmonar. De todos estos 218 ó sea 70%, reaccionaron positivamente; la mayor proporción (79.2%) fué entre casos de segundo período. De 265 personas sospechadas de tuberculosis 35.9% reaccionaron y de 127 pacientes que sufrían otras enfermedades 14.1% reaccionaron. Finalmente, de 185 individuos que se suponían en salud, 18.3% reaccionaron. Del numero total 15.2% eran niños menores de 15 años? Por todo hubo 24 casos de reacción fuerte, 10 de las cuales duraron más de cinco días. En un paciente escrofuloso sobrevino un caso de keratitis. Diez y ocho por ciento de la segunda instilatión en el ojo opuesto produjeron reacción, y 100% de ellas en el mismo ojo. La prueba cutánea fué subsecuentemente aplicada en 52 casos y la subcutánea en 89 seguidas por un considerable aumento en el percentage de las reacciones positivas en las clases sospechosas.

Las conclusiones son:

1. Las pruebas con tuberculina en la conjuntiva verificadas con soluciones débiles con una simple instilación tienen algun valor para confirmar la presencia de la tuberculosis en los estados incipientes.

2. Tienen poco valor cuando los sinomas de tuberculosis indican solo una sospecha.

3. No ha sido todavía determinado su valor para distinguir la tuberculosis "activa latente" de la tuberculosis cicatrizada, en personas aparentemente en salud.

4. La repetición de la prueba en el mismo ojo no tiene ventaja sobre las pruebas cutáneas y subcutaneas, y puede extraviar al investigador y ser peligrosa.

5. La repetición en el otro ojo segun el método del autor, ofrece tan poca ventaja que no puede recomendarse.

6. La reacción de la conjuntiva no se digna de confianza por la prognosis.

7. Con uso de las precauciones propias el peligro del ojo es pequeño y no debe impedir la prueba cuando no son aplicables otros métodos, como cuando se presenta fiebre.

Debe restringirse á los aduotos puesto que la prueba cutánea se ha encontrado de igual valor para los niños y es inofensiva.

8. Las pruebas cutáneas con el simultáneo uso de tuberculina diluida y fuerte ofrece un método que revela inmediatamente, ó excluye, la infección tuberculosa, sin peligro ni inconveniente. Se necesita experiencia para monstrar el valor de este método.

9. Las pruebas subcutáneas deben restringirse á aquellos casos en que se desea la reacción focal y cuando resultan negativas las otras pruebas.

SUR L'OPHTALMO-REACTION À LA TUBERCULINE.

By Fernand Arloing,

Lyon, France.

Depuis la communication de Wolff-Eisner faite à la Société de Médecine berlinoise, le 15 Mai 1907, et depuis celle de M. Calmette à l'Académie des Sciences le 17 Juin, 1907, la méthode nouvelle utilisant la réaction conjunctivale à la tuberculine pour dépister la tuberculose chez l'homme a été l'objet d'un nombre si considérable de publications, et a servi de point de départ à tant de recherches qu'il est impossible de songer à en donner un aperçu bibliographique.

Je crois préférable de réunir ici les particularités concernant l'ophtalmo-réaction que j'ai pu observer personnellement dans les domaines de la clinique humaine, de l'expérimentation pure, ainsi que les observations comparatives d'oculo-réaction et de séro-réaction agglutinante bacillaire selon la méthode de S. Arloing et P. Courmont.

I. Faits Cliniques.

Je me suis attaché surtout à l'étude clinique de l'opthalmo-réaction, dans un travail publié en collaboration avec M. Dumarest. Nous y insistons sur les diverses modalités de la réaction conjonctivale:

A côté des réactions nettement positives, et des réactions franchement négatives, il existe les réactions douteuses où l'observateur même le plus averti se trouve dans l'impossibilité d'affirmer ou de nier absolument l'existence du phénomène. Ces réactions douteuses sont assez fréquemment observées dans la pratique pour constituer dans une certaine mesure un point faible de la méthode. Nous insistons également sur le moment d'apparition et sur la durée de la congestion oculaire. Ainsi nous distinguons des réactions normales apparaissant de la dixième à la douzième heure, les réactions hâtives, très franches dès deux heures après l'instillation et les réactions retardies qui ne se dessinent jusqu'après 24 à 48 heures.

Nous avons également attiré l'attention, dans ce travail, sur un point très important: un malade n'ayant pas présenté une opthalmo-réaction à une première épreuve peut parfaitement réagir lors d'une deuxième ou même seulement lors d'une troisième instillation de tuberculine.

Quatre cas semblables sur 40 se sont presentés au cours de nos premièrs essais. Nous les avions parfaitement constatés. Aussi éliminant comme

raison d'être de ces irrégularités réactionelles un vice opératoire nous écrivions: "D'ailleurs la réaction oculaire progressivement croissante chez certains sujets est là pour témoigner que le phénomène en question rélève d'autre chose que d'une faute grossière de technique." Si nous n'avons pas prononcé pour expliquer ce fait le mot qui a été dit depuis de "sensibilisation conjonctivale, d'anaphylaxie locale," qu'il me soit du moins permis de constater que parmi les premiers nous avons signalé la chose et noté la particularité d'une telle constatation.

Mais la réaction conjonctivale ne se donne pas toujours à un phénomène exclusivement local, elle peut s'accompagner de phénomènes concomitants, desquels je vais parler.

Dans le même travail déja cité, j'ai montré, avec Dumarest, que l'instillation de tuberculine peut éveiller chez le tuberculeux une réaction générale (lassitude, courbature, malaise vague, céphalée, troubles digestifs) et une réaction thermique.

Au moment où nous les avons signalés, de tels phénomènes généraux étaient niés par les promoteurs de la méthode et par ces premiers propagateurs. Après notre travail, des faits confirmatifs de notre opinion ont été publiés par Audéoud, par Baur, par Henri Dufour. Cet auteur a publié des courbes thermiques qui rapprochées des notres forment un ensemble démonstratif.

La fièvre peut s'allumer le jour même, le lendemain ou le surlendemain de l'instillation et la température monter de deux degrés, ou de 0.6° à 0.8°.

Les réactions thermiques ne sont pas intenses le plus souvent. Quant à leur cause, il ne faut pas la rechercher exclusivement dans la conjonctivité artificielle puisque des réactions oculaires très faibles s'accompagnent d'une élévation de température, mais bien plutôt l'attribuer à l'action général de la tuberculine sur l'organisme du tuberculeux, puisque le poison bacillaire s'absorbe facilement au niveau de la muqueuse oculaire.

Un symptôme oculaire sur lequel il a été dit peu de choses, est celui que nous avons signalé, consistant en une dilatation pupillaire de l'oeil tuberculiné. Ce symptôme n'a pas en lui même de valeur spéciale, mais d'après nos observations il rencontre assez fréquemment, dans 10 à 15 pour cent des épreuves, et nous ne l'avons jamais vu signalé avant nous. Depuis on l'a discuté quoiqu'il en soit cette mydriase diminue après 24 à 48 heures, parfois il suivit de beaucoup à la disparition de la rougeur conjunctivale. Elle semble surtout le fait des réactions vives.

Le mécanisme de ce symptôme est très vraisemblablement corrélatif de l'action vaso-dilatatrice propre de la tuberculine. Le pouvoir qu'a cette toxine de retacher les fibres circulaires des vaisseaux et des capillaires se traduit de cette façon au niveau du muscle irien.

Par la suite, j'ai pu constater sur certains sujets du myosis pupillaire au

cours de la réaction mais beaucoup moins souvent que la mydriase. En somme, il faut savoir que l'oculo-réaction peut également provoquer des phénomènes pupillaires associés dépourvus en réalité de toute gravité et de toute signification.

L'emploi de plus en plus fréquent de l'ophtalmo-diagnostic par la tuberculine dans la pratique journalière a soulevé des craintes au sujet de l'influence que pourrait exercer sur une réaction oculaire éteinte des injections sous cutanées thérapeutiques de tuberculine.

Ce rappel possible de l'oculo-réaction a paru constituer pour S. Lévy une contreindication à l'utilisation de la méthode de Wolff-Eisner comme moyen révélateur ou à l'institution chez un sujet ayant subi au préalable l'épreuve oculaire d'une cure ultérieure par la tuberculine.

J'ai vu que les injections de tuberculine provoquent presque toujours ce reveil de la congestion conjonctivale, mais que ce rappel n'a pas une intensité et une durée capables de me faire rallier aux conclusions de S. Lévy.

J'ai constaté également qu'un traitement antérieur prolongé à la tuberculine n'imprime pas une allure particulière à l'oculo-réaction. Dans ces conditions, cette dernière a été tantôt très marquée, tantôt légère, sans règle précise. Enfin, l'imprégnation par un sérum antitoxique, antituberculineux, qui pourtant neutralise la tuberculine *in vitro*, n'a pas anuulé chez le malade, les effets de la tuberculine déposée sur la conjonctive.

Très discutée et très brûlante est la question des accidents provoqués par l'ophtalmo-réaction. On peut dire qu'actuellement une forte majorité de médecins reconnaissent que l'oculo-diagnostic ne joint pas de cette innocuité absolue qu'on se plaisait à affirmer au début de son emploi.

Pour ma part, en dehors des réactions particulièrement prolongées ou violents, j'ai pu constater dans mes observations personelles ou dans mon entourage des accidents réels. Je ne peux les rapporter ici; ils sont réunis dans la thèse que j'ai inspirée à M. De Comboury et dans un travail en collaboration avec ce dernier, publié dans le Journal de Physiologie et de Pathologie générale. Entre autres, j'ai noté de la kèratite limbique avec ulcérations marginales cornéennes, de la kèratite phlyctenulaire, deux ulcérations de la cornée, de l'épésclerité généralisé. Ceci montre que le qualificatif d'inoffensif est loin de la réalité clinique, car ces faits sont bien peu nombreux à côté de ceux semblables qu'on a apporté de tous côtés. Je serait plus exact de dire que l'ophtalmo-réaction est un procédé commode de diagnostic, mais en retenant qu'il peut être suivi de complications locales capables d'entrainer des altérations serieuses de la vision.

D'autres auteurs ont insisté sur les inconvénients moraux qu'elle présente pour le malade. Cet effet psychique est certain. Je peux citer deux observations dè que Dufour apelle "la neurasthènie consecutive à la réaction oculaire."

Il est bien entendu que toutes les précautions d'asepsie doivent être prises, que la solution de tuberculine doit être avantageusement abaissée jusqu'à $\frac{1}{190}$ ou $\frac{1}{200}$, que l'intégrité de l'oeil instillé doit être vérifiée au préalable. Malgré cela des symptômes ennuyeux peuvent se produire. En dehors des moyens proposés pour les combattre, je me suis trouvé assez bien de l'application toutes les 8 heures d'une collyre à l'adrénaline au 3000e.

Je ne parlerais pas des suites éloignées de l'ophtalmo-réaction au point de vue ophtalmologique pour n'ayant par de documents sur ce sujet.

II. Faits Expérimentaux.

Certaines remarques m'ont frappé en dépouillant les observations d'ophtalmo-réactions positives à la tuberculine se produisant chez des malades non tuberculeux cliniquement. En particulier, la constance et l'allure speciale de la conjonctivite tuberculinique chez les typhiques m'ont fait émettre l'hypothèse que le phénomène de Wolff-Eisner se produisait surtout chez des individus en état "d'intoxinisation," c'est à dire dont l'organisme est imprégné et sensibilisé par une toxine quelconque à condition qu'elle jouisse de propriétés vaso-dilatatrices. En effet, l'oculo-réaction est réductible à un acte organique vaso-moteur. Il est produit par une toxine vaso-dilatatrice, la tuberculiné, chez un subjet dont les centres nerveux vaso-dilatateurs sont sensibilisés par une intoxinisation tuberculineuse et préparés de ce chef à réagir à des incitations périphériques du même ordre.

Un grand nombre de toxines microbiennes possedant un pouvoir vaso-dilatateur analogue à celui de la tuberculine, je pouvais espérer développer expérimentalement l'aptitude à réagir à la tuberculine instillée sur la conjonctive chez des animaux non tuberculeux, mais imprégnés par ces diverses toxines. De ces expériences communiquées à la Société de Biologie, il résulte que des lapins non tuberculeux intoxiqués progressivement avec de la tuberculine, et avec les toxines du bacille d'Eberth, de staphylocoque et du bacille diphtérique, ont présenté des oculo-réactions positives au cours de ces diverses imprégnations toxiniques.

Donc, ces diverses toxines, toutes vaso-dilatatrices, ont été capables de créer chez ces lapins indemnes de tuberculose l'aptitude à réagir localement à la tuberculine. A la phase moyenne de ces intoxinisations, l'oculo-réaction s'est manifestée avec le plus de fréquence et le plus d'intensité. La toxine éberthienne a développé la capacité réactionnelle à la tuberculine d'une façon plus active que la tuberculine elle-même. C'est là un fait important, et il semble qu'il suffise à expliquer les oculo-réactions positives et intenses, presque la règle en clinique chez les typhiques, sans invoquer la présence constante de quelques bacilles tuberculeux dans leurs ganglions mesentériques.

La toxine diphtérique paraît également jouir du même pouvoir. Quant

à la toxine staphylococcique, ses effets analogues se développent plus lentement et plus faiblement.

Par contre, à cette phase de l'expérience où les intoxications tuberculinique et éberthienne plus chroniques commençaient à développer un état d'immunisation contre leurs effets, la réaction conjonctivale a décliné en intensité et en netteté, l'avantage restant alors à la tuberculine.

Cette atténuation, et même la disparition de la réaction locale oculaire à la tuberculine, lorsque l'organisme est saturé par ce poison, a été bien décrite par MM. Calmette, Breton et Petit.

Donc, à un moment donné d'une imprégnation toxinique, des sujets non tuberculisés ont offert une réaction oculaire positive qui aurait pu faire conclure à tort à l'existence d'une tuberculose en évolution. L'oculo-réaction à la tuberculine n'est donc pas spécifique. Elle n'a pas une valeur révélatrice absolue.

Dans d'autres recherches, j'ai constaté que deux chevaux producteurs de sérum antidiphtérique, et en cours d'immunisation depuis plus de douze ans ont presenté une oculo-réaction positive à la tuberculine. Deux autres chevaux fournissant du sérum antitétanique ont eu également des réactions positives mais moins marquées que les précédentes. Ces réactions s'expliquent, en l'absence de toute infection tuberculeuse, par le mécanisme mis en lumière dans les expériences précédentes; toutefois la toxine tétanique parait moins apte que la toxine diphtérique à éveiller cette susceptibilité réactionelle.

On voit donc que l'oculo-réaction à la tuberculine peut exister chez l'animal, das les conditions d'intoxinisation spéciales, en l'absence de toute lésion tuberculeuse en évolution ou latente. L'oculo-réaction n'est donc pas une méthode de diagnostic ayant une valeur clinique, spécifique et absolue. Il m'a été possible de mettre en lumière chez l'homme l'aptitude à la réaction conjonctivale créé par certaines infections autres que la fièvre typhoïde. Aussi chez 10 syphilitiques examinés, les malades arrivés à la pleine efflorescence de la période secondaire ont eu des réactions positives; les porteurs de chancre induré n'ont rien présénte après la tuberculination oculaire. Mais dans tous ces cas, il est à remarquer que la réaction a été lente, tardive comme si, spécificité tuberculeuse faisant défaut, la conjonctivité ne se produisait qu'à raison de la sensibilisation nervomotrice du malade par son infection *totius substantiæ* résultant du virus syphilitique.

Par la suite, des observations analogues viendront probablement renforcer cette manière de voir. Récemment M. Baur dans un article de la Revue de la Tuberculose (Juin 1908) a fait la constatation suggestive suivante: Sur 6 malades atteints d'ictère et non tuberculeux, 5 ont des ophtalmo-réactions positives. L'auteur ajoute que ces observations d'ictèriques, réagissant positivement à l'instillation du tuberculine, sont pour lui absolu-

ment superposables, aux faits expérimentaux que j'ai signalés. Evidemment, tous ces constatations portent une atteinte à la valeur spécifique absolue de l'oculo-réaction. Néanmoins, dans la pratique médicale, une ophtalmo-réaction positive à la tuberculine est une grave présomption en faveur de la tuberculose; par contre, on ne peut pas éliminer d'une façon certaine l'infection bacillaire du sujet au cas de réaction négative, de l'aveu même des plus ardents défenseurs de la méthode.

C'est entendu que l'emploi de la tuberculine reste un ces meilleurs procédés scientifiques sinon le meilleur pour diagnostiquer une infection tuberculeuse même très légère. Mais les preuves abondent que la réaction tuberculinique pratiquement considerée comme spécifique ne l'est pas en sens rigoureux du mot. Il y a dans ces réactions à considérer deux facteurs, l'agent provocateur, et l'aptitude à réagir. Pour peu que l'on examine attentivement ces questions, on ne peut s'empêcher de penser que la facteur qui emporte sur l'autre est l'apparition chez le sujet de l'aptitude à réagir qui se developpe sous l'influence de telle ou telle infection bien définé. Si alors, chez un tel sujet prêt à la réaction, en raison de son infection spécifique, on fait agir un poison microbien homologue, on obtient la réaction maxima. Des toxines hétérologues seront elles aussi capables bien souvent de provoquer un phénomène réactionnel d'analogue au premier, mais qui ne saurait, dans ce dernier cas, être qualifié de spécifique. Dans cet ordre d'idée, un travail récent de Lüdmersen et Glenny (1) est très remarquable. Ces auteurs ont obtenu des réactions à la malléine thermiques et locales, chez des chevaux non morveux mais qui étaient imprégnés avec de la toxine diphtérique, ou d'autres produits microbiens tuberculine, produits solubles du bacillus coli, de l'Eberth, du streptocoque, du staphylocoque, pyocyanique etc. Dira-t-on après cela que la malléine donne des réactions diagnostiques d'une valeur absolue? Non, cela est impossible comme pour la tuberculine; mais en pratique, la malléination a néanmoins une grande valeur.

Les recherches de Schick sur la cuti-réaction à la toxine diphtérique chez les enfants diphtériques et tuberculeux et celles de Gutz sur les réactions certaines cutanées obtenues avec n'importe quelle toxine, ne viennent elles pas confirmer mes expériences. Gutz a vu que 75% des tuberculeux ont une réaction cutanée positive par la tuberculine et 50% une réaction positive avec d'autres toxines. Sur 126 enfants 68.4% ont réagi à la tuberculine, 42.1% à la toxine diphtérique, 36.8% à la toxine paratyphique. Il dit encore que, dans d'autres recherches, 60% d'enfants tuberculeux ont réagi à la tuberculine aussi qu'aux toxines diphtériques et typhiques, et 40% à la toxine paratyphique.

Telles sont les idées que je voulais exposer sur le mécanisme et la valeur de l'oculo-réaction. Ont peut donc conclure que la réaction oculaire à la tuberculine révèle dans la grande majorité des cas une infection tuberculeuse.

Elle peut également se produire chez des individus non tuberculisés mais en état "d'intoxinisation," c'est à dire dont l'organisme est imprégné et sensibilisé par une toxine quelconque jouissant de propriétés vaso-dilatatrices. L'oculoréaction n'aurait donc pas une valeur absulue au point de vue, théorique, mais seulement une valeur relative.

III. Etude Comparative de l'Oculo-réaction et de la Séro-réaction Agglutinante Bacillaire.

Il est venu à l'idée de divers observateurs de mettre en parallèle les renseignements (sur la valeur définitive desquels il a fallu souvent déjà revenir) fournis par les réactions cutanée et oculaire.

De ces recherches, il est difficile de conclure pour l'une ou l'autre méthode, bien que l'oculo-diagnostic semble l'emporter en sensibilité—peut-être excessive d'ailleurs—sur le cuti-diagnostic.

Quoi qu'il en soit, de telles observations se bornent à constater la capacité réactionnelle plus ou moins grande d'un sujet soupçonné de bacillisation tuberculeuse vis-à-vis d'un seul et identique agent provocateur de cette réaction, la tuberculine. En réalité, les faits accumulés dans cet ordre d'idées démontrent exclusivement l'influence que la voie d'introduction de la tuberculine dans un organisme tuberculeux peut exercer sur l'aptitude de cette toxine à provoquer ultérieurement une réaction révélatrice.

Il ne nous apparaît pas que ces recherches, dites comparatives, puissent être envisagées comme une critique de la valeur séméiologique de l'une ou de l'autre méthode, puisque, nous le répétons, l'agent essentiel de la réaction est le même dans les deux cas; seul le mode d'introduction varie. Ces considérations m'ont suggéré, d'essayer parallèlement en collaboration avec M. Dumarest, la séro-agglutination bacillaire suivant le procédé de S. Arloing et P. Courmont et l'ophtalmo-réaction à la tuberculine. Dans ces conditions, il devenait intéressant de voir si la réaction humorale et la réaction oculaire donneraient des réponses concordantes ou divergentes, de confronter, dans une certaine mesure, les renseignements diagnostiques que fournissent chez un malade suspect de tuberculose la recherche de sa sensibilité à la tuberculine et du pouvoir agglutinant de son sérum vis-à vis du bacille de Koch.

A cet effet nous avons soumis, avec M. Dumarest, des malades du sanatorium d'Hauteville (Ain), à ces deux procédés. Or, ces essais parallèles ont donné les chiffres suivants. Sur 40 cas:

La Séro-réaction a été:		L'Ophtalmo-réaction a été:	
Positive	31 fois.	Positive	25 fois.
Négative	4 —	Négative	6 —
Douteuse	5 —	Douteuse	9 —

Cela revient à dire que, si l'appréciation clinique avait été subordonnée à la constatation de l'un ou de l'autre de ces signes, on aurait pu affirmer la tuberculose 31 fois avec le séro-diagnostic et 25 fois seulement avec l'oculo-diagnostic. Par contre, il aurait fallu conclure à la non-spécificité dans 6 cas d'ophtalmo-réaction contre 4 cas de séro-réaction. Le doute, enfin, eût existé 9 fois après l'essai oculaire et 5 fois après l'essai humoral.

Le séro-diagnostic a été positif, en contradiction avec une ophtalmo-réaction, négative, dans 4 cas: une tuberculose osseuse et pulmonaire guérie; une tuberculose fibreuse non en évolution; une tuberculose fibro-caséeuse parenchymateuse bien localisée et peu évolutive mais non guérie et une fibreuse progressive.

Inversement, nous avons pu voir, mais plus rarement et avec moins de netteté, l'oculo-réaction plus affirmative que la séro-réaction.

D'autre part, trois malades n'ont réagi qu'à une seconde instillation; ce qui fait réfléchir sur les inconstances de la méthode.

J'ai receuilli avec M. De Camboury une nouvelle série d'observations cliniques, que je poursuis journellement d'ailleurs, dans lesquelles l'ophtalmo-réaction et la séro-réaction ont été faites simultanément.

Ces observations sont réunies en trois groupes principaux qui comprennent.

A. Les affections cliniquement tuberculeuses.

B. Les affections cliniquement non tuberculeuses.

C. Les maladies infectieuses aiguës ou chroniques. Voici les résultats.

A. Affections Cliniquement Tuberculeuses.

De 49 observations de malades cliniquement tuberculeux à différentes périodes on est autorisé à conclure:

1. Au stade III, réaction oculaire manque rarement (2 fois sur 12). La fréquence de la séro-réaction est presque aussi grande. Néanmoins les résultats fournis par les deux méthodes semblent être en raison inverse les unes des autres, c'est-à-dire qu'à une ophtalmo-réaction très positive, correspond, en général, une séro-réaction plus faible et *vice versa;*

2. Aux stades I et II, les deux procédés donnent des indications très sensiblement concordantes;

3. Dans les formes aiguës (forme pneumonique, congestion aiguë, granulie) l'ophtalmo-réaction est positive et la séro-réaction négative. Cette absence de réaction humorale a toujours été constatée par S. Arloing et P. Courmont dans les circonstances cliniques semblables;

4. Dans les pleurésies, l'ophtalmo-réaction s'est montrée plus fréquente que la séro-réaction. Il faut toutefois noter que la nature tuberculeuse des épanchements pleuraux n'a pas toujours été démontrée. Pourtant, à défaut de l'inoculation du liquide, la formule leucocytaire a été recherchеé. Des

mononucléoses pleurales ont coïncidé avec une oculo-réaction négative laquelle a été positive avec une formule polynucléaire;

5. Dans les formes chroniques à évolution lente et bénigne, ou marchant vers la guérison, ou dans les tuberculoses locales, les deux réactions sont en raison inverse l'une de l'autre; mais ici l'oculo-réaction est presque toujours négative alors que la séro-réaction est positive.

B. Affections Cliniquement non Tuberculeuses.

1. Dans 17 cas où la tuberculose n'était pas cliniquement appréciable, et où l'élément infectieux aigu ne jouait pas un rôle prépondérant, l'oculo-réaction a été positive sept fois, négative dix fois;

2. La séro agglutination a donné 5 résultats positifs et 3 négatifs; neuf fois le sérum sanguin a fait preuve d'un léger pouvoir agglutinant permettant soupçonner par cette nuance une tuberculisation legère du sujet.

3. Dans l'hypothèse d'une tuberculose latent à rélever par l'emploi de ces deux procédés, la séro-réaction apparaitrait donc comme plus délicate que l'oculo-réaction.

C. Maladies Infectieuses Aiguës ou Chroniques.

1. Les affections rhumatismales aiguës donnent des réactions positives avec les deux méthodes;

2. Les affections rhumastismales chroniques ne réagissent pas aussi régulièrement à la tuberculine, mais présentent très souvent une séro-réaction positive;

3. Au cours de l'infection typhique, une ophtalmo-réaction positive, très intense et rapide dans son apparition est pour ainsi dire la règle. Le sérum des typhiques est simultanément capable d'agglutiner les bacilles tuberculeux. Toutefois, l'intensité de la réaction humorale est proportionnellement moindre que celle de la réaction oculaire.

L'examen de tous ces faits permet de conclure en faveur de la séro-réaction bacillaire agglutinante plutôt qu'en faveur de l'oculo-réaction. Nous n'hésitons pas à accorder à la réaction humorale la priorité dans l'échelle de la valeur séméiologique des deux procédés et cela pour les raisons suivantes:

1. La réaction humorale est plus constante relativement à l'ensemble des cas.

2. Elle est plus nuancée, dans un même cas. Chez les mêmes malades, au cours de recherches prolongées plusieurs années, elle suit une curieuse évolution en rapport avec les phases de la maladie et de la résistance du sujet. De ce chef, elle prend une certaine valeur pronostique.

3. Elle est plus constante au même moment d'une évolution morbide.

4. Elle est plus certainement inoffensive, en tout cas moins désagréable pour le patient.

Je terminerai cette étude par quelques considérations sur les causes et la signification des réactions oculaire et humorale.

Les matériaux qui ont été réunis vont-ils permettre un essai d'interprétation de la valeur de l'ophtalmo-réaction à la tuberculine.

Un fait se dégage nettement dès l'abord. L'ophtalmo-réaction, qui a été présentée essentiellement comme un moyen de diagnostic d'une valeur clinique absolue et infaillible, ne permet pas de révéler à coup sûr la tuberculose partout où elle existe. En cela l'ophtalmo-réaction est devenue l'égale des diverses autres méthodes qui pas plus qu'elle, sur le terrain biologique et clinique, ne sauraient prétendre à l'infaillibilité.

En effet, l'ophtalmo-réaction n'existe pas dans tous les cas où les symptômes cliniques et la réalité tangible qu'est le bacille de Koch, constaté dans les sécrétions du malade, permettent d'affirmer la tuberculose, et cela sans que son absence puisse être imputée à la défaillance des forces réactionnelles de l'individu.

Par contre, elle s'observe dans un grand nombre d'affections où la tuberculose ne saurait être suspectée comme agent causal, ce qui, pour certains, témoignerait de sa sensibilité à une tuberculose cliniquement latente.

Nous réservons pour plus tard la question de la fréquence de l'oculo-réaction dans les maladies aiguës infectieuses.

D'un autre côté, que devons-nous dire de la séro-agglutination bacillaire?

En ce qui concerne les tuberculoses pulmonaires caractérisées, elle est présente dans les cas où S. Arloing et P. Courmont ont dit l'avoir rencontrée, c'est-à-dire dans la grande majorité des cas, non dans tous. Elle manque, en effet, chez les cachectiques ou dans les cas de tuberculisation aiguë. Une séro-réaction positive constitue en somme un signe de grande probabilité d'une tuberculose en évolution ou latente, mais une séro-réaction négative n'autorise pas à conclure à l'absence de toute lésion tuberculeuse.

A nos yeux, l'ophtalmo-réaction à la tuberculine et la séro-réaction bacillaire ne présentent donc pas plus l'une que l'autre une valeur séméiologique absolue. Elles ne sauraient permettre, au cas où elles sont négatives, de nier la tuberculose, et même au cas où elles sont positives, il s'agit de savoir si elles donnent la certitude d'une infection tuberculeuse, à l'exclusion de toute autre infection.

Leur signification, d'une façon générale, est peut-être différente. C'est du moins ce que l'examen de nos observations nous autorise à supposer.

Plus instructives à ce point de vue sont, en effet, les divergences entre ces deux procédés de diagnostic que la concordance de leurs résultats, car ces divergences semblent fournir un aperçu sur le mécanisme intime de ces deux phénomènes et leur donner leur vraie signification.

Il est curieux, à tout prendre, de voir ces deux méthodes, dont le but est de montrer la tuberculose là où elle existe mais où quelquefois on est peu enclin

à la soupçonner, être parfois l'une positive, l'autre négative chez un même sujet dûment infecté par le bacille de Koch.

Aussi, frappés par des faits si opposés en apparence, tendons-nous à attribuer à l'ophtalmo-réaction et à la séro-réaction bacillaire une signification différente.

Comme j'ai montré plus haut *l'ophtalmo-réaction témoignerait de l'intoxication de l'organisme par la tuberculine;* elle serait donc un moyen d'apprécier "l'intoxinisation" du sujet. La *séro-réaction serait la preuve*—ainsi qu'on l'admet en général pour les réactions agglutinantes—*de la réaction de défense de l'économie et son intensité mesurerait le degré d'immunisation du sujet* par le fait de sa résistance à l'action du bacille de la tuberculose.

Dès la constatation des contradictions apparentes entre ces deux moyens d'investigation clinique j'avais émis cette idée. J'écrivais avec M. Dumarest, que l'hypothèse, qui envisagerait le pouvoir agglutinant du sérum d'un malade comme l'expression de la réaction de défense de son organisme et en ferait un phénomène parallèle de l'immunisation, semble théoriquement acceptable et peut s'étayer sur toute une catégorie de faits d'apparence assez homogène. Je me demandais aussi d'autre part, si on était autorisé à considérer la réaction oculaire ou autre à la tuberculine, comme une manifestation de sensibilité spécifique préparée, exaltée même, par la tuberculinisation lente de l'organisme et trahissant plutôt l'imprégnation toxique que l'immunisation.

Cette dualité des phénomènes d'intoxication par les toxines d'un microbe et des réactions d'immunisation de l'individu sous l'influence de ce même microbe et de ses poisons peut s'observer dans de nombreuses affections, et ces faits sur lesquels nous reviendrons tout à l'heure nous serviront à étayer notre interprétation.

Mais à ne considérer que la *tuberculose pulmonaire,* ne voit-on pas les *formes aiguës,* où l'empoisonnement tuberculineux est à son maximum, présenter une réaction oculaire positive intense tandis que le pouvoir agglutinant du sérum est nul.

S'il s'agit de *formes à évolution chronique* plusieurs cas sont à considérer.

Lorsque le sujet subit les premières atteintes du bacille de Koch, grâce aux toxines qu'il sécrète, on voit apparaître, l'aptitude de la conjunctive à réagir à cette même toxine tuberculeuse. Ces conditions productrices de l'oculo-réaction ont été bien démontrées expérimentalement par M. Calmette et ses élèves. A ce moment, la réaction d'auto-immunisation de l'organisme n'a pas eu le temps de se reproduire et la séro-réaction est négative. Mais que le processus infectant progresse, de pair avec l'intoxinisation tuberculeuse s'affirme la réaction d'immunisation et l'on voit apparaître le pouvoir agglutinant dans le sérum.

Suivant la forme de la maladie, suivant le degré et le mode de réaction de

chaque malade, suivant la virulence et le pouvoir toxinogène du bacile infectant, l'oculo-reaction prime en intensité la séro-réaction ou *vice versa*, ou l'une est presque absent par rapport à l'autre très accusée.

Suivant aussi l'évolution de la tuberculose vers une issue favorable ou au contraire fatale, les réactions oculaire ou humorale ont la préséance l'une sur l'autre. La réaction humorale se recontre surtout très intense dans les cas favorables, et peut avoir, par conséquent, une valeur pronostique intrinsèque réelle, que ne posséderait pas pour nous, à un égal degré, l'ophtalmo-réaction. L'examen des faits cliniques fournit une grande vraisemblance à ces hypothèses.

Restent les *affections tuberculeuses à bacilles atténués* ou certaines maladies chroniques de l'appareil respiratoire où la tuberculose a pu être en ligne à un moment donné, mais s'est éteinte en provoquant un certain degré d'immunité du sujet. Là on trouve, comme par exemple dans un cas de gommes tuberculeuses cutanées, une ophtalmo-réaction négative et une séro-agglutination très positive. Ce cas ne réunit-il pas en clinique les conditions requises expérimentalement pour vacciner un animal contre la tuberculose, à savoir un bacille peu virulent et peu toxinogène, un bacille atténué, comme S. Arloing l'a montré exister depuis longtemps et si fréquemment dans les tuberculoses locales.

Ou bien a-t-on affaire à un emphysémateux de vieille date chez qui, dans un passé déjà ancien, on a pu trouver de la tuberculose, la séro-agglutination aura des chances d'être positive et l'ophtalmo-réaction négative.

Les résultats auxquels je suis arrivé avec M. P. Courmont en recherchant l'oculo-réaction et la séro-réaction chez les vieillards sont confirmatifs.

L'inverse se produit dans les pleurésies, maladies essentiellement prédisposantes à l'infection tuberculeuse pulmonaire ultérieure.

Voici quelques remarques faciles à faire sur le parallélisme ou la discordance des deux méthodes. Evidemment, il ne saurait être question de règles fixes dans une maladie où les périodes de résistance de l'économie ou de victoire de l'agent infectant se succèdent comme dans la tuberculose et d'aussi variable façon.

Mais à un moment donné de l'évolution d'une tuberculose, une ophtalmo-réaction positive et une séro-réaction négative nous semblent d'un *pronostic* douteux. L'inverse indiquerait une évolution favorable. Une intensité quasi-égale des deux phénomènes prouverait que l'organisme est dans un état d'équilibre indifférent de réaction, susceptible d'évoluer vers la guérison ou de subir des influences défavorables.

Rarement la séro-réaction et l'oculo-réaction sont en contradiction pour un même malade au cours de diverses *affections non tuberculeuses* et peu infectieuses par leur nature. Mais dans ces cas, la réaction agglutinante est, en général, plus fréquente que la réaction oculaire. Ceci signifierait que ces

divers malades infectés à une période de leur existence par un bacille atténué en ont triomphé en s'immunisant, d'où leur pouvoir agglutinant positif, mais comme leur imprégnation toxinique est nulle, ils ne possèdent pas l'aptitude à la réaction oculaire.

En l'espèce, l'oculo-réaction dirait peut-être mieux la vérité quant à un processus tuberculeux actuel que la séro-réaction dont la réponse serait susceptible, jusqu'à un certain point, d'induire en erreur un clinicien non rompu à son interprétation.

Notre hypothèse, qui ferait de la réaction de Wolff-Eissner et Calmette une preuve d'intoxinisation en général et de la réaction de S. Arloing et P. Courmont celle d'une immunisation de l'organisme, reçoit, il faut l'avouer, une très apparente confirmation si l'on examine ce qui se passe au cours de la *fièvre typhoïde* par exemple.

Tous les auteurs qui ont appliqué l'ophtalmo-réaction à la tuberculine chez des typhiques sont unanimes à proclamer la constance, la netteté, la violence même des réactions conjonctivales chez de tels malades indemnes de tuberculose. Or, la dothiénentérie est une maladie où l'intoxication aiguë par les toxines microbiennes est de plus accusée.

Mais par contre, cette infection provoque un processus d'immunisaton d'autant plus actif et d'un pronostic d'autant plus favorable que la réaction agglutinante de Widal atteint un taux plus élevé, ainsi que l'a bien montré P. Courmont. Aussi, sans nier la spécificité des agglutinines microbiennes, il est certain que ces agglutinines typhiques peuvent agir dans des limites moindres sur d'autres microbes, en particulier sur le bacille de Koch. Ceci explique pourquoi à côté de l'oculo-réaction positive on rencontre une séro-réaction bacillaire positive elle aussi. Cette question très délicate est encore à réserver.

Toutefois les deux phénomènes existent simultanément, leurs causes productrices intimes et nécessaires étant remplies. On doit remarquer pourtant que l'ophtalmo-réaction à la tuberculine semble plus facile à éveiller et partant d'une constatation plus banale que le pouvoir agglutinant, puisque la réaction oculaire est pour ainsi dire à son maximum d'intensité chez les typhiques alors que la réaction agglutinante bacillaire est présente certes, mais plus discrète dans sa manifestation, moins trompeuse par conséquent.

Il est donc fort à présumer, pour ne pas dire certain, que dans la majeure partie des infections microbiennes comportant du fait de leur évolution naturelle des phénomènes d'intoxication et d'immunisation, les mêmes réactions démonstratives de ces processus existeront, elles aussi.

De cela il faut rapprocher ce que j'ai dit, au début de ce travail, de l'oculo-réaction dans la syphilis.

De tout ce qui précède, il ne faudrait pas conclure que je dénie toute valeur diagnostique spécifique vis-à-vis de la tuberculose aux deux procédés

qui ont été comparé. Ils se rencontrent avec leur maximum d'intensité et de constance chez des sujets tuberculisés, mais pourtant leurs réponses ne doivent pas fournir autre chose qu'un élément de grande probabilité au cas de réaction positive, et encore ne sont-elles pas sans appel. Ces deux réactions ont leur signification propre sur laquelle nous ne revenons pas.

La séro-agglutination bacillaire de S. Arloing et P. Courmont peut exister dans des affections autres que la tuberculose, mais à part les cas d'infection typhique, elle garde selon nous une valeur révélatrice plus grande que l'ophtalmo-réaction, car un taux d'agglutination élevé se rencontre d'une façon élective surtout au cours de la tuberculose confirmée ou latente.

Quant à l'ophtalmo-réaction elle ne possède pas cette spécificité absolue qu'on s'est plu à lui accorder. Il est évident que la tuberculine semble *mieux adaptée* à faire réagir des sujets intoxiqués par la toxine homologue, mais cela ne constitue pas, je le répéte, la spécificité dans le sens rigoureux du mot et n'assure pas l'infaillibilité de ses arrêts.

Conclusions.

1. L'ophtalmo-réaction est un procédé de diagnostic commode dans son application, mais dont la valeur séméiotique n'est *pas absolue*, puisqu'elle existe dans des infections autres que la tuberculose, la fièvre typhoïde, la syphilis, etc.;

2. Elle est *inconstante*, puisqu'elle fait défaut quelquefois dans le cas de tuberculose confirmée. Elle ne permet pas de séparer à coup sûr les sujets tuberculeux de ceux qui ne le sont pas;

3. Elle *n'est pas toujours inoffensive*. Les réactions générales qu'elle provoque sont peu graves; mais il n'en est pas de même des réactions oculaires qu'elle engendre et qui peuvent entraîner des altérations, parfois irrémédiables, de la vision;

4. Comparée à la séro-réaction agglutinante bacillaire, elle ne s'est pas montrée supérieure à cette dernière, qui, en tout cas, aurait l'immense avantage d'être à coup sûr inoffensive, plus constante et plus nuancée;

5. Il semble que l'ophtalmo-réaction, d'une façon générale, témoigne plutôt du degré d'intoxication de l'organisme par différents poisons microbiens, tandis que la séro-réaction mesure plutôt ses forces défensives vis-à-vis de l'infection.

BIBLIOGRAPHIE DES TRAVAUX LYONNAIS CONCERNANT L'OPHTALMO-RÉACTION ET LA CUTI-RÉACTION.

I—Ophtalmo-réaction.

Fernand Arloing et Dumarest: "L'ophtalmo-réaction à la tuberculine. Les modalités. Phénomènes concomitants. Emploi de l'adrénaline au cours des symptômes congestifs de la réaction, Essai parallèle avec la sero-réaction," Province médicale, No. 41, 12 octobre, 1907.

Fernand Arloing: "Ophtalmo-réaction à la tuberculine dans quelques cas de syphilis," Comptes rendus de la Société médicale des Hôpitaux de Lyon, 3 décembre, 1907, et Lyon Médical, No. 2, 12 janvier, 1908, tome cx, p. 97.

Fernand Arloing et G. Debornbourg: "Etude comparative sur l'ophtalmo-réaction à la tuberculine et la séro-réaction agglutinante bacillaire," Journal de physiologie et de pathologie générale, 19 janvier, 1908.

Fernand Arloing: "Essai sur le mécanisme de l'oculo-réaction à la tuberculine. L'oculo réaction est-elle specifique," Comptes rendus de la Société de Biologie, séance du 29 janvier, 1908, année 1908, tome i, p. 128.

Fernand Arloing: "Nouvelles considérations sur le mécanisme et la valeur spécifique de l'oculo-réaction à la tuberculine," Comptes rendus de la Société de Biologie, séance du 2 mai, 1908, année 1908, tome i, p. 722.

Fernand Arloing: "Oculo-réaction et tuberculino-thérapie," Comptes rendus de la Société médicale des Hôpitaux de Lyon, séance du 23 juni, 1908.

Fernand Arloing: Voir Paul Courmont.

Fernand Arloing: Voir J. Nicolas.

Bonnet: "Ophtalmo-réaction à la tuberculine," Comptes rendus de la Societé nationale de médecine de Lyon, séance du 29 novembre, 1907; et Lyon Médical, No. 52, 29 décembre, 1907, tome cix, p. 1123.

Bonnet et Bérard: "Ophtalmo-réaction de Calmette dans les maladies cutanées et vénériennes," Comptes rendus de la Societé nationale de Médecine de Lyon, séance du 2 décembre, 1907; et Lyon Médical, No. 4, 26 janvier, 1908, tome cx, p. 189.

Bonnet: "Oculo-réaction sans tuberculose," Societé nationale de Médecine de Lyon, séance du 9 mars, 1908; et Lyon Médical, No. 14, 5 avril, 1908, tome cx, p. 772.

Paul Courmont, Fernand Arloing, et Bérard: "Comparaison de l'oculo-réaction et de la séro-réaction bacillaire chez les vieillards," voir: Comptes rendus de la Societé médicale des Hôpitaux de Lyon, séance du 23 juni, 1908.

Jean Lépine: "Ophtalmo-réaction de Calmette en psychiatrie," Comptes rendus de la Societé de Biologie, séance du 27 juillet, 1907, tome ii, 1907, p. 244.

Jean Lépine et R. Charpenel: "Nouvelles recherches sur l'ophtalmo-réaction chez les alierées, Comptes rendus de la Societé de Biologie, séance du 12 octobre, 1907, tome ii, 1907, p. 301.

Jean Lépine: "Ophtalmo-réaction en psychiatrie—Variations et anomalies," Comptes rendus de la Societé de Biologie, séance du 19 octobre, 1907, tome ii, 1907, p. 331.

Lesieur, J. Chalier, Gardère, et Bonnet: "Oculo-réaction tuberculeuse—200 cas (enfants, vieillards, convalescents, etc.)," Comptes rendus de la Societé médicale des Hôpitaux de Lyon, séance du 19 novembre, 1907; et Lyon médical, No. 49, 8 décembre, 1907, tome cix, p. 967.

J. Nicholas, Fernand Arloing, et P. Gauthier: "Ophtalmo réaction et séro-réaction chez les lupiques." Comptes rendus de la Societé médicale des Hôpitaux de Lyon, séance du 30 juni, 1908.

II—Cuti-reaction.

Fernand Arloing: "Sur la réaction cutanée à la tuberculine," Comptes rendus de la Societé médicale des Hôpitaux de Lyon, séance du 18 juni, 1907; et Lyon médical, No. 41, 13 octobre, 1907, tome cix, p. 626.

Fernand Arloing: "Réaction cutanée provoquée par diverses tuberculines et par le sérum d'hommes tuberculeux," Comptes rendus de la Societé de Biologie, séance du 29 juni, 1907.

Fernand Arloing: "Sur la cuti-réaction à la tuberculine." Comptes rendus de la Societé de Biologie, séance du 27 juillet, 1907, tome ii, 1907, p. 247.

Fernand Arloing: "Réaction cutanée à la tuberculine dans la tuberculose experimentale du veau et du chien," Comptes rendus de la Societé de Biologie, séance du 23 novembre, 1907, tome ii, 1907, p. 499.

J. Nicholas et P. Gauthier: "Cuti-réaction et ophtalmo-réaction dans diverses dermatoses d'origine tuberculeuse ou non," Comptes rendus de la Societé médicale des Hôpitaux de Lyon, séance du 19 novembre, 1907, et Lyon médical, No. 52, 29 décembre, 1907, tome cix, p. 1138.

Journal of Hygiene, viii, No. 1, Janvier, 1908.

Sobre la Reacción Oftálmica de la Tuberculina.—(ARLOING.)

En esta comunicación el autor se limita a reportar solamente los hechos personales, clínicos y experimentales.

Bajo el punto de vista clínico, él estuvo en coloboracion con M. Dumarest, uno de los primeros en llamar la atención sobre los fenómenos térmicos y generales consecuentes a la instilación de la tuberculina en el ojo. Algunas veces él ha observado la reacción de la conjuntiva acompañada de una mas ó menos marcada dilatación de la pupila; con menos frecuencia miosis fué observada bajo las mismas circunstacias. En sus primeras investigaciones él también observó, sin poder dar entonces una explicación definida, un fenómeno que el lo consideró como una anafilaxis local, esto es, que un paciente en el cual la reacción fué negativa en la primera instálación de la tuberculina, la reacción fue positiva en la segunda ó tercera prueba.

Con relación á la acción interna de la tuberculina y la reacción ocular, la previa reacción ocular con las inyecciones subcutáneas en el tratamiento por medio de la tuberculina; mas esto no constituye una indicación contraria al empleo de los dos métodos en la misma persona. También parece que una inpregnación previa del paciente de tuberculina, usada como medida terapéutica, tiene un efecto variable en las reacciones oculares subsecuentes.

La reacción ocular no está exenta de peligro. Esta eva algunas veces acompañada de complicaciones, tales como conjuntivitis y ulceraciones de la córnea. La previa instilación de 1 al 3000 de adrenalina es capaz de contrarestar ciertas reacciones violentas y una reacción prolongada.

En la segunda comunicación de sus trabajos, Fernand Arloing dá los resultados de sus experimentos sobre el mecanismo patogénico de la tuberculina y la reacción ocular; conejos no tuberculosos impregnados con la toxina de ciertos microbios (tifoidea, stafilococus, difteria) dieron una reacción ocular positiva. El conejo fue mas sensible á la toxina tifoidea que á la tuberculina ó ambas presentaron una reacción igual. De la misma manera la reacción fué positiva en los caballos destinados á la producción de sueros antidifteríticos y antitetánicos.

Estos hechos experimentales, que demuestran una reacción ocular positiva en las personas no tuberculosas, está de acuerdo con los casos clínicos que presentan una reacción positiva en personas ifectadas de tifoidea, stafilococus, sífilis ú otras infecciones. Basado sobre estas dos series de observaciones, Fernand Arloing creé que la reacción ocular de la tuberculina, la cual representa una reacción vaso-motora, puede ocurrir con cualquira toxina cada vez que los centros vaso-motores del individuo esten en condiciones de reactuar á la dilatación de los vasos. Por lo tanto la reacción ocular de la tuberculina ocurre en los individuos que están en un estado de intoxicación, esto es, en aquellos en los cuales el organismo

está impregnado de una toxina cualquiera. La reacción ocular, por lo tanto, no es de carácter específico en un sentido teorético, sino que ésta tiene solamente un valor relativo.

En la tercera parte de este artículo, el autor hace un estudio comparativo sobre la reacción ocular y el fenómeno de la aglutinación del microbio á la acción del suero. Estas dos reacciones (aglutinación del bacilo y la reacción ocular) se encuentran con frecuencia en el mismo individuo, una de ellas puede estar ausente en la presencia de la otra ó finalmente una puede ser mas intensa que la otra.

El estudio de los síntomas y el curso clínico de estos casos de una reacción contradictoria ha dado lugar, en la opinión del autor, á atribuir un valor diferente a la reacción oftálmica de aquel que pertenece al suero. La reacción oftálmica indica que el organismo esta intoxicado de tuberculina; por otra parte la reacción del suero, así como la aglutinación por el suero, puede considerarse como una reacción de defensa de la economía, mientras que la intensidad de la reacción representa el grado de inumidad del individuo al bacilo de la tuberculosis.

Esto parece, por lo tanto, que en la práctica, á cierto punto de la evolución de la enfermedad, una reacción oftálmica positiva con una reacción negativa del suero, indica un pronóstico dudoso: mientras que lo contrario un pronóstico favorable. Si los dos fenómenos presentan una intensidad igual, demuestra que el organismo está en un estado de equilibrio indiferente, y que la enfermedad puede terminar favorable ó que el enfermo sucumbe a las condiciones desfavorables.

Tal es la significación que Fernand Arloing atribuye a la reacción ocular, mas una conclusion positiva no puede dársele á un problema tan complicado.

En resumen:—La reacción ocular es un procedimiento fácil y conveniente para el diagnóstico; ésta falta agunas veces en personas afectadas de tuberculosis, y por otra parte, esta puede ocurrir en pacientes afectados de una afección distinta. Su valor en el diagnóstico, aunque muy considerado al presente, no es sinembargo absoluto, mas aún, la prueba no está exenta de complicaciones. La reacción ocular no parece ser superior á la aglutinación del bacilo á la accion del suero, la cual tiene la ventaja de ser absolutamente sin peligro, más constante y más delicada. Finalmente, la reacción oftálmica representa mas bien el estado de intoxicación del organismo; mientras que la reacción del suero revela las fuerzas utilizables en a defensa contra la infección.

On the Ophthalmo-reaction to Tuberculin.—(ARLOING.)

In this communication the author has confined himself to the report of personal clinical and experimental facts.

From the clinical standpoint, he was, in collaboration with M. Dumarest, one of the first to call attention to the thermic reaction and the general phenomena that follow the instillation of tuberculin into the eye. In some cases he has seen the conjunctival reaction accompanied at the time by more or less marked dilatation of the pupil; much more rarely myosis was observed under the same circumstances. In his earliest researches he also observed, without at the time offering any explanation, a phenomenon which he regarded as a kind of local anaphylaxis, namely, that a patient in whom the ophthalmo-reaction was negative at the first instillation, may react to a second, or even a third, test.

With regard to the interaction of tuberculin treatment and the ocular test, it appears that a previous ocular reaction is frequently revived by the subcutaneous injection of medicinal doses of tuberculin; but this does not constitute a contraindication to the employment of the two procedures in the same subject. It also appears that a previous impregnation of a patient with tuberculin for therapeutic purposes has a very variable effect on a subsequent ocular test.

The ocular reaction is not free from danger. It is occasionally accompanied by ocular complications, such as prolonged conjunctivitis and ulcerations of the cornea. The previous instillation of 1 : 3000 adrenalin is capable of counteracting certain excessively violent or prolonged reactions.

Arloing, in the second part of his communication, gives the result of his experimental researches on the pathogenic mechanism of the ocular reaction to tuberculin: Non-tuberculous rabbits impregnated with various microbic poisons (tuberculin, typhoid, staphylococcus and diphtheric toxins) gave positive ocular reactions. The rabbit was, in fact, more actively sensitized by the typhoid toxin than by tuberculin, or at least to an equal degree. In the same manner horses used for the production of antidiphtheric and antitetanic serum reacted positively under certain conditions.

These experimental facts, which show that a positive ocular reaction to tuberculin may be obtained in non-tuberculous subjects, accord with the clinical cases of positive reactions in the non-tuberculous suffering from typhoid, staphylococcic, syphilitic, or some other infection. On the strength of these two series of observations, Fernand Arloing believes that the ocular reaction to tuberculin, which represents a local vasomotor reaction, may occur whenever the vasomotor centers of an individual are in a condition to react by vasodilatation by reason of their being impregnated with a microbic toxin. Hence the ocular reaction to tuberculin occurs in individuals who are in a state of intoxication, *i. e.*, whose organism is impregnated and sensitized by a toxin of any kind. The

ocular reaction is therefore not absolutely specific from a theoretical sense, but has merely a relative value.

In the third portion of his paper the author takes up a comparative study of the ocular reaction and the bacterial serum-agglutination test.

These two reactions are often found in the same individual; while, on the other hand, one may be present when the other is absent; or, finally, one may be more intense than the other.

The study of the symptoms and of the clinical course in these cases of contradictory reactions has led the author to attribute a different value to the ophthalmo-reaction from that which belongs to the serum-reaction. The ophthalmo-reaction indicates that the organism is intoxicated with tuberculin; the serum-reaction, on the other hand, like agglutination reactions, is generally recognized as showing a defensive reaction of the economy, while the intensity of the reaction measures the degree of immunity of the individual to the tubercle bacillus.

It appears, therefore, that in practice, at a certain point in the evolution of a tuberculous disease, a positive ophthalmo-reaction with a negative serum-reaction indicates a doubtful prognosis; while the contrary would indicate a favorable outcome. When the two phenomena are practically equal in intensity, it shows that the organism is in a state of indifferent equilibrium and that the disease may either end in recovery or the patient succumb to unfavorable influences.

Such is the significance which Fernand Arloing attributes to the ocular reaction, but no positive conclusion can be drawn in such a complicated question.

To sum up, the ocular reaction is a convenient and easily available diagnostic procedure; it sometimes fails in patients who are certainly tuberculous; and, on the other hand, may occur in subjects not suffering from a bacterial infection. Its diagnostic value, although quite considerable in practice, is nevertheless not absolute. The test is not always harmless. It has not proved itself superior to the bacillary serum-agglutination, which has the advantage over the ocular test of being absolutely harmless, more constant, and more delicate. Finally, the ophthalmo-reaction is an indication rather of the degree of intoxication of the organism, while the serum-reaction reveals the forces available for defense against the infection.

THE USE OF THE DIFFERENTIAL CUTANEOUS REACTION IN THE DIAGNOSIS, PATHOLOGY, AND THERAPY OF TUBERCULOSIS.

By Dr. Ladislaus Detre,

Director of the Jenner-Pasteur Institute and of the Tubercular Department of the Charité-policlinic, Budapest.

---

1. By the aid of the differential cutaneous reaction, recommended by me in 1907 (detailed description in the Wiener klinische Wochenschrift, 1908), it is possible to gain, in different ways, a right idea of the biological conditions of tubercular patients. This reaction is an addition to von Pirquet's method, and consists in the use of three substances which, by means of von Pirquet's skin inoculation, are introduced at the same time into the same part of the skin:

(*a*) Concentrated old tuberculin.

(*b*) Filtrate of a culture of the human bacilli.

(*c*) Culture of bovine filtrate.

2. The presence of the single papules makes it possible to distinguish, first, the difference between the cases toxin susceptible and toxin non-susceptible; second, between human and bovine susceptible.

3. The toxin susceptible individuals, characterized by large infiltration papules, are mostly found in incipient cases, but you will also find them in older cases with well-preserved reaction qualities. On the contrary, the toxin susceptibility occurs very frequently in surgical tubercular cases, even of old standing. All so-called "pretuberculosis" cases, where the well-known toxic symptoms prevail, show a high degree of toxin susceptibility, whereby I understand, under the term toxins, those changeable filtrate substances which are destroyed during the concentration of the bouillon into old tuberculin. The older the tuberculosis, the quicker disappears the susceptibility for the toxin filtrate. Finally, there remains a very slight susceptibility only for the proteins (endotoxins) contained in the old tuberculin. The chronicity of tuberculosis depends entirely upon the toxin tolerance.

4. Reactions made on individuals at intervals produced the same unvarying cutaneous picture.

Weak reactions, however, became sometimes more distinct through inoculations applied several times, as already proved by von Pirquet.

On the other hand, special outside circumstances will produce considerable change in the cutaneous picture in either one of the two possible extremes. It will happen that a strong reaction, characterized by large papules, may be followed by the formation of small papules, and a reaction scarcely perceptible in the beginning, may increase to considerable intensity.

5. Initially strong reactions in adults may decrease in the following cases:

(*a*) When the disease eliminates itself naturally, or when the tuberculous process comes to a relative standstill.

(*b*) When a sudden inundation of the organism, by the tubercular poisons, occurs, or when tuberculosis expands suddenly, or when generalization of miliary tuberculosis begins.

(*c*) When a successful immunization against poisons has been established.

In the first case we find that patients have a feeling of good spirits and comfort, without any local signs of bacilli. In the second, general weakness, fever, and an increased number of bacilli. In the third, a feeling of health, lack of subjective symptoms of disease, increased weight, but, in spite of all, the increase of bacilli to enormous numbers.

Persons belonging to this last division are the ones I wish to call "chronic carriers" of tubercle bacilli.

6. An increase of intensity of the originally hardly noticeable rudimentary cutaneous reaction is being created—

(*a*) Whenever a latent infection, of older origin, manifests itself all of a sudden, for instance, through well-known influences favoring tuberculosis in general, as colds, influenza bacilli, or pneumococci, etc.

(*b*) When, during the first immunization treatment, the method of applying the remedies has not proved successful, on account of a hasty increase of the doses, or when a wrong toxin was given, and the result obtained was not immunity, but intolerance. The following are the cases which produced the symptoms of subcutaneous reactions as known of old, a local reaction at the site of the faulty injection, general symptoms of intolerance (with the very same signs of intoxication which the patient experienced in the beginning of his sickness), feeling of oppression, emaciation, lack of appetite, an accelerated pulse, insomnia, headache, anemia, etc., and, in harmony with this syndrome, the reappearance of the skin papules that had vanished long ago.

7. Therefore the cutaneous reaction acts as an indicator of the human organism, a fact I wish to emphasize in opposition to some investigators who, proceeding with entirely wrong analogies, are inclined to see in the picture produced by other chemical and bacteriological toxins only incidental symptoms of the cutaneous reaction.

8. By my method we succeed in separating tuberculous individuals into two different groups, viz., human and bovine sensitives, according to the way they react upon human and bovine filtrates, with a stronger papule. Tuberculins are not advisable for the purpose of these experiments, although similar, yet less intensive, differences may appear after the use of these protein-like substances. Therefore only the filtrates I recommend ought to be employed.

It is interesting, indeed, to notice similar differential symptoms following the ophthalmic reaction (A. Kovacs)* in the chronic slight toxin sensitive as well as, particularly, in the incipient highly toxin sensitive cases.

I distinguish the larger, often more noticeable, "predominant papule" from the "concomitant papule," and I must emphasize that both filtrate papules oftentimes show scarcely any difference from each other.

9. The investigations of the human-bovine question, started in May, 1907, and continued to the present time, show conclusively that—

(*a*) The quality of the cutaneous reaction, in repeated investigations, is constant in this respect that a human case never later on shows a picture of a bovine reaction.

(*b*) That the tubercular patients, after subcutaneous injections of either toxin, possess a good deal of tolerance against the toxin which produced slight papules, or none at all, but no tolerance whatsoever against the predominant filtrate. In simultaneous hypodermic injections of both filtrates (in both arms, for instance) the predominant filtrate will produce, in $\frac{1}{100}$ to $\frac{1}{1000}$ part of a dose, for instance ($\frac{1}{10000000000}$ part of a drop), a local reaction of inoculation or an infiltration, a redness, while the other non-predominant filtrate will produce a toxin effect only in larger quantities. Besides, it can be demonstrated that, on introduction of both toxins at right intervals, the organism can only with great difficulty be immunized against the predominating filtrate because of its quickly appearing intolerance symptoms.

The organism is intolerant against the predominant filtrate.

(*c*) By means of the Bonome method of precipitation we can demonstrate in the blood-serum of the human susceptible cases precipitins against the proteins of the human bacillus, while the blood-serum has very little influence on the bovine proteins. In the bovine susceptible cases we find the opposite result.

10. My own investigations and experiments, corroborated since by V. Berend, Hein, and John, and, lately, by V. Gebhardt, have conclusively demonstrated that pulmonary tuberculosis, in more than 90 per cent. of the

* Unpublished experiments and observations made by Dr. Kovacs in Budapest Dispensary.

cases, shows a preponderance of the human reaction, while in visceral and surgical cases, in adults, the bovine reaction, in almost one-third to one-half, can be found. This opinion is held by a good many authorities who consider the human bacillus a factor in surgical tuberculosis.

11. The human bovine susceptibility ought to be established in the following cases:

(*a*) For the purpose of arriving at a differential diagnosis and ascertaining some hygienically most important questions in regard to the cause and modus of infection, namely, inhalation (?) or ingestion (?). In two cases, for instance, we were led to the diagnosis of "intestinal tuberculosis due to the use of raw milk" only by the establishment of the bovine reaction.

(*b*) For the purpose of investigating the scientifically most important question of the dualism. Here I wish to emphasize that analogous experiments made on tuberculous cattle brought forth the same expected result, *i. e.*, that the bovine filtrate showed a much more outspoken reaction in these animals than the human substances.

(*c*) For the purpose of answering the question of origin or type of bacilli spores, or tuberculins, respective filtrates, also emulsions which, with the help of "selected test persons," *i. e.*, human or bovine sensitives, can be solved with great ease within twenty-four to forty-eight hours. These experiments were made by me with prompt results in different tuberculins.

(*d*) By everybody who intends to try a therapeutic toxin immunization with the dualistic view. Spengler, as well as myself, arrived at the same conclusion that the greater number of tuberculars can be easily immunized with the "concomitant toxin," but that they are found very intolerant against the predominant filtrate. Therefore the cutaneous reaction influences the therapist in the choice of the toxin he is going to use, and, for that reason, prevents the untoward effects which are apt to follow the employment of a non-suitable and intolerable toxin. The injection of the concomitant toxin causes, in many instances, the disappearance of intoxication symptoms, while the predominant filtrate causes an accentuation of these symptoms. The complementary or concomitant filtrate produces toxin immunity. The predominant, to the contrary, intolerance. These conditions remind us of the fact that we can, without detriment to the organism, establish immunization with the aid of modified toxins, the so-called "toxoids," as, for instance, in the case of the tetanus bacillus, while we encounter untoward sequels if we immunize with a non-modified toxin.

12. The systematic pursuit of the differential cutaneous reaction makes it possible, of course, under strict observation of the clinical history of the case, to execute the therapeutic toxin immunization more easily and surely than with any other previously known method. Its execution is simple, its results visible, certainly noticeable easier than the results of the opsonin

test. The differential cutaneous reaction is to be recommended to everybody who tries to ascertain the biological conditions of the tubercular afflicted and to influence the tubercular process by immunization.

Die Anwendung der differentiellen Kutanreaktion in der Diagnose, Pathologie und Therapie der Tuberkulose.—(DETRE.)

1. Die differentielle Kutanreaktion des Autors, eine Modifikation von Pirquet's Vorgang, besteht in der Applikation dreier verschiedener Substanzen auf die Haut: (*a*) Konzentrirtes Alt-Tuberkulin. (*b*) Filtrat einer menschlichen Tuberkel-Bacillen-Kultur. (*c*) Filtrat einer Rinderkultur.

2. Einteilung der Fälle in (*a*) giftempfindliche und giftunempfindliche, (*b*) human- und bovinempfindliche.

3. Giftempfindliche Individuen hauptsächlich unter frühen Fällen gefunden, auch in älteren Fällen mit guter Reaktion, und ganz häufig in alten chirurgischen Fällen.

Chronische Tuberkulose lediglich von Toleranz gegen die Gifte abhängig.

4. Bei Wiederholung des Versuchs in kurzen Zwischenräumen ständiges kutanes Bild; schwache Reaktion durch Wiederholung deutlicher, die Reaktion charakterisiert durch grosse Papeln, möglicherweise eine mildere Eruption, oder die Reaktion steigt von Null zu unbestimmter Intensität.

5. Bei Erwachsenen ist eine zuerst starke Reaktion, oft durch verschiedene Faktoren vermindert:

(*a*) Spontane Kur;

(*b*) Plötzliches Übergreifen von Miliar-Tuberkulose;

(*c*) Auftreten von Immunität.

6. Eine zuerst leichte oder rudimentäre Reaktion kann intensiv werden:

(*a*) Wenn eine latente Infektion plötzlich manifest wird.

(*b*) Im Laufe einer Immunisations-Behandlung.

Fälle dieser Art entwickeln das Bild der Tuberkulin-Reaktion: Lokale Reaktion und allgemeine Symptome. Wiedererscheinen der längst verschwundenen Toxinpapel.

7. Das Kutanbild ist ein Indikator der Empfindlichkeit des Organismus.

8. Nach des Autors Methode werden die Tuberkulösen in zwei Gruppen, die human- und bovinempfindliche, eingeteilt. Für diesen Zweck soll man eher Filtrat-Kulturen als Tuberkuline verwenden.

Bei wenig Giftempfindlichen und mehr Giftempfindlichen Unterscheidung der "dominanten Papel" von der "Begleitpapel."

9. Seit Mai, 1907, bezüglich der "Human-Bovin-Fragen" folgende Ergebnisse:

(*a*) Kutanbild bleibt nach wiederholter Untersuchung qualitativ dasselbe, d. h., ein "Human-Fall" bietet später nicht das Bild der bovinen Reaktion.

(*b*) Wenn beide Toxine subcutan injiziert werden, zeigt sich eine grössere Toleranz, welcher eine leichte oder negative Papel-Formation entspricht. Andererseits sind sie gegen das dominante Filtrat ausserordentlich intolerant. Bei gleichzeitiger Injektion beider Filtrate kann das dominante lokale Reaktionen hervorrufen, selbst wenn die Dosis 100,000 mal kleiner ist. Wenn die Injektionen zu verschiedenen Zeiten gemacht werden, kann der Organismus nur mit grösster Schwierigkeit gegen das dominante Filtrat immunisiert werden. Der Organismus ist intolerant gegen das dominante Filtrat.

(*c*) Im Blutserum der human-empfindlichen Fälle Präcipitine gegenüber den Proteinen des Human-Bacillus nachgewiesen (Bonome'sche Präcipitationsmethode). Den Bovin-Protinen gegenüber ist das Blutserum bloss wenig wirksam.

10. Des Autors eigene Untersuchungen zeigen, dass die Lungentuberkulose in mehr als 90% der Fälle ein Überwiegen der Human-Reaktion ergiebt, dagegen bei Visceral- und chirurgischen Fällen die Bovin-Reaktion in fast ein Drittel bis zur Hälfte der Fälle nachweisbar.

11. Feststellung der Human-Bovin-Empfindlichkeit vorzunehmen:

(*a*) Zur Sicherung schwieriger Diagnosen und Lösung wichtiger hygienischer Fragen (Inhalation? Ingestion?).

(*b*) Zur Erforschung der Frage des Dualismus.

(*c*) Zur Beantwortung der Frage über Provenienz des Typus Bacillus oder Tuberkulin.

(*d*) Wenn man einen Patienten für Heilzwecke mit den Toxinen beider Typen von Bacillen immunisieren will. Die Mehrzahl der Tuberkulösen kann mit einem Begleitgiftstoff leicht immunisiert werden, während sie dem dominanten Filtrat gegenüber intolerant bleibt. Das Begleit-Filtrat verursacht Gift-Immunität, das dominante dagegen Intoleranz.

12. Ausübung der differentiellen Kutanreaktion erlaubt unter peinlicher Beobachtung des klinischen Krankheitsbildes; die therapeutische Gift-Immunisierung leichter und sicherer als bisher möglich. (Siehe Punkt 5.) Einfache Ausführung, objective Resultate sicherer als Opsonin-Bestimmung.

El Uso de la Reacción Cutanea Diferencial en el Diagnostico, la Patologia y el Tratamiento de la Tuberculosis.—(Detre.)

1. La reacción diferencial cutanea del autor, que es una modificacion del procedimiento de von Pirquet, consiste en la aplicacion simultanea a la piel de tres sustancias diferentes, despues de haber aplicado el metodo

de von Pirquet: (*a*) vieja tuberculina concentrada, (*b*) el filtro de una cultura del bacilo de la tuberculina de origen bovino, (*c*) el filtro de una cultura del bacilo de origen bovino.

2. Division de los casos en (*a*) aquellos que son sensitivos a la toxina (positivos) y aquellos que no lo son (negativos); y (*b*) los casos positivos á la tuberculina de origen humano y casos positivos a la tuberculina de origen bovino.

3. Los individuos que dan una reaccion positiva se encuentran entre los prematuros; tambien casos mas avanzados con una buena reaccion. En cuanto mas avanzado sea el proceso, tanto mas rapida la reaccion desaparece. La tuberculosis cronica depende enteramente sobre la tolerancia de la toxina.

4. Cuando la prueba se aplica á cortos intervalos la reaccion cutanea es constante; reacciones poco marcadas puden hacerse mas distintas por medio de la repeticion de la prueba. Una modificacion del cuadro de la reaccion cutanea, sinembargo, se manifiesta; asi una reaccion marcado, caracterizada por largas papulas puede ser reemplazada por una reaccion ligera, ó la reaccion puede aumentar desde nula á un grado de conciderable intensidad.

5. En los adultos una reaccion primaria marcada puede ser disminuida por medio de diferentes causas: (*a*) Una cura espontanea ó detención del proceso; (*b*) una invasion repentina del organismo de los productos tuberculosos (tuberculosis miliar); (*c*) por medio de la inmunidad.

6. Una reaccion primaria ligera o rudimentaria puede ser aumentada:—(*a*) por medio de la aparicion repentina de previas infecciones latentes, como despues de un resfrio, tromatismo fisico y moral, trabajo exesivo, influenza, infeccion del neumococo, etc. (*b*) Esta reaccion puede ser aumentada durante el curso de la enfermedad cuando el tratamiento de la inmunizacion es hecha con dosis inapropiadas e intolerables. Casos de esta clase se desarrollan en el cuadro familiar de la reaccion de la tuberculina; una reaccion local en el punto de la inoculacion, sintomas de una intolerancia general particularmente sintomas de intoxicacion tales como indisposicion, falta de apetito, aumento en la frecuencia del pulso, insomnia, dolor de cabeza, anemia, etc., y la reaparicion de la erupcion debida á la toxina despues que esta habia desaparecido por largo tiempo.

7. Los sintomas cutaneos son una indicacion de la sensibilidad del organismo.

8. Segun el metodo del autor, los individuos tuberculosos pueden dividirse entre dos grupos: Aquellos que son positivos a la toxina de origen humano y aquellos que son positivos a la toxina del bacilo de origen bovino. Con este objeto, las cultures filtradas son recomendado en vez de la tuberculina. El autor hace distincion de las "pápulas dominantes" que se observan

en los casos cronicos con una reaccion ligera, y en particular á los casos positivos iniciales, y las pápulas "concomitantes," la diferencia entre las dos, sinembargo, es muy pequeña.

9. Las investigaciones hechas desde Mayo de 1907, con relacion á la cuestion humana-bovina demuestra: (*a*) que el cuadro cutaneo permanece cualitativamente el mismo despues de repetidas examenes, esto es, un "caso humano" no demuestra mas tarde la reaccion bovina. (*b*) Cuando ambas toxinas se inyectan simultaneamente, el individuo demuestra una tolerancia mayor á la toxina que corresponde á la formacion de unas ligeras papulas ó á la ausencia de estas: mientras que por otra par ellas son extremadamente intolerantes al filtrado dominante. En la inyeccion simultanea de los dos filtrados, el filtrado dominante puede producir una reaccion local con infiltracion y enrojecimiento, aun cuando la dosis es 100,000 veces mas pequenas (1:100,000,000 eg.; mientras que el otro filtrado debe ser aplicado en cantidades considerables para que este produzca el mismo efecto. Cuando las inyecciones se hacen en diferentes tiempos, el organismo puede ser inmunizado al filtrado dominante con gran dificultad solamente, por que este produce rapidamente sintomas de intolerancia. El organismo es intolerante al filtrado dominante. (*c*) El suero dela sangre en los casos positivos á la tuberculina del bacilo de origen humano, contiene precipitantes para las sustancias nitrogenadas del bacilo de origen humano (metodo de Bonnome), mas tiene muy poca accion contra las sustancias nitrogenadas del bacilo de origen bovino. Lo contrario se observa en los casos bovinos positivos.

10. Las investigaciones del autor, confirmadas por Berend, Heim, John y Gebhardt, demuestran que mas de un 90% de los casos de tuberculosis pulmonar exhiben una preponderancia á la reaccion humana; mientras que en los casos quirurgicos y viserales, en los adultos, la reaccion bovina pude demonstrarse en una tercera parte o en la mitad de los casos.

11. La reaccion dela toxina humana o bovina debera ser determinada bajo las condiciones siguientes: (*a*) Para confirmar un diagnostico dificil, y dar explicacion a ciertas caracteres higienicos en cuanto á la propagacion y el modo de la infeccion (inhalacion ó ingestion); (*b*) En el estudio de la individualidad del bacilo dela tuberculosis, El ganado reacciona mas vigorosamente al filtrado bovino que al filtrado humano. (*c*) En dar una base en cuanto al origen ó tipo del bacilo, ó tuberculinas (ó filtrados), lo cual puede hacerse entre veinte y cuatro ó cuarenta y ocho horas por medio de la seleccion de la prueba individual de acuerdo con la reaccion a la tuberculina humana o bovina. (*d*) Cuando se desea inmunizar a un paciente con objeto terapeutico, a la toxina de los dos tipos del bacilo. La mayor parte de los individuos tuberculosos pueden facilmente ser inmunizados con las toxinas concomitantes, y son intolerantes al filtrado dominante; por lo tanto el terapeutico debera escojer la substancia que debera emplearse por medio

del cuadro cutaneo, y de este modo evitar los efectos posteriores desagradables que algunas veces acompana á las toxinas inapropiadas. El filtrado concomitante produce la inmunidad á la toxina, mientras que el dominante produce intolerancia.

12. Por medio del uso sistematico de las diferentes reacciones cutaneas, es posible inmunizar a un paciente contra a toxina, esto es por supuesto, cuando los sintomas clinicos son guardados bajo una extricta observacion con mas facilidad y seguridad que ha side posible hasta el presente. El tecnisismo es mas simple, los resultados son objectivos y mas seguros y mas facilmente preservados que los resultados del metodo de la opsonina. La reaccion cutanea diferencial es recomendada a otros investigadores que deseen obtener un conocimiento de la condicion interior en cuanto á la patologia de los pacientes tuberculosos, y á los que se esfuerzan influenciar los procesos tuberculosos por medio de la inmunizacion.

VALEUR PRONOSTIQUE DE L'OPHTALMO ET DE LA CUTI-RÉACTION.

By Dr. S. Irimescu,
Bucarest, Rumania.

Dans l'Hôpital des tuberculeux de Filaret, j'ai essayé l'ophtalmo-réaction à partir du mois de Juillet 1907 jusqu'au 1er. Avril 1908 sur 176 malades, appartenant presque tous au IIIème degré, d'après la classification de Turban et ayant tous des bacilles dans les crachats.

J'ai employé d'abord, la tuberculine preparée selon la technique de Calmette—précipitation par l'alcool—mais pour la plupart des cas je me suis servi de la tuberculine de Koch, en solution à 1% dans l'eau boriquée à 3%. La solution était renouvelée tous les huit jours pour empêcher son altération.

Comme premier fait que je tiens à signaler c'est que chez aucun de ces malades je n'ai pu constater les phénomènes graves d'irritation oculaire, signalées dans quelques cas par d'autres auteurs. Chez tous la réaction s'est presenté avec les caractères habituels. Elle a été plus ou moins marquée suivant les cas observés et a évolué dans les délais normaux.

Parmi ces 176 malades, 34 ont réagi d'une façon peu marquée (1er degré), 73 d'une façon prononcée (IIème degré), 23 d'une façon intense (IIIème degré), 46 enfin d'entre eux n'ont pas réagi du tout.

En défalquant de ces malades ceux à lésions très prononcés—IIIème degré d'après la classification de Turban—j'ai pu constater que 18 d'entre eux ont réagi au IIIème degré (intensément), 49 au IIème degré (d'une façon moyenne), 28 au Ier degré (d'une façon faible) et que 33 n'ont réagi d'aucune façon.

D'un autre côte les malades à lésions moins prononcées ont tous réagi: de 23 malades au IIème degré de la maladie, 3 ont réagi d'une façon intense, 17 ont eu une réaction moyenne, et 3 une réaction faible; et de 7 malades au premier degré de la maladie, 2 ont réagi intensément, 2 ont eu une réaction moyenne et 2 autres une réaction faible. Une seule des malades au premier degré de la maladie a eu l'ophtalmo-réaction négative.

En faisant le pourcentage des malades au IIIème degré de la maladie qui ont presenté une ophtalmo-réaction positive j'ai pu donc constater que 68.2% d'entre eux ont réagi à la tuberculine introduite par la voie oculaire.

La proportion de ces malades à ophtalmo-réaction positive est donc beaucoup plus elevée, dans ma statistique que dans les statistiques données par d'autres auteurs.

C'est ainsi que Wolff-Eisner chez 18 malades au IIIème degré n'a pu constater une réaction positive que dans 28% des cas. Albert Fränkel sur un nombre encore plus petit des malades, dans 45% des cas. Ma statistique porte, il est vrai, sur un nombre beaucoup plus elevé des malades—128 malades au IIIème degré—et les résultats obtenus sont à ce point de vue là très proches de ceux publiés récemment par Roepke[1] qui dans 51 cas au IIIème degré a trouvé la réaction positive dans 47% des cas après la première instillation, et 43% des cas après la seconde instillation.

Ce qui fait qu'après 2 instillations 90.2% des malades ont réagi à la tuberculine.

L'importance de l'ophtalmo-réaction comme moyen de diagnostic est aujourd'hui généralement reconnu. Pour les malades à lésions avancées, tels que la majorité de ceux reçu à l'hôpital de Filaret, le diagnostic ne faisait aucune difficulté, d'autant plus que tous avaient les bacilles dans les crachats. J'ai cherché alors de me rendre compte de la valeur de l'ophtalmo-réaction comme moyen d'établir le pronostic de la maladie. D'après Wolff-Eisner, Teichmann, Stadelmann, la réaction négative chez les malades à lésions avancées montre que l'organisme n'est plus en état de réagir contre les toxines du bacille tuberculeux, ce qui impliquerait un pronostic défavorable. Une réaction positive montrerait par contre que l'organisme peut résister à ces toxines, qu'il dispose par conséquence des moyens de lutte, sans qu'on puisse préjuger cependant qui de l'organisme ou du bacille aura la victoire.

Il existe en effet des nombreux cas avancés—ma statistique le montre—oú la réaction est positive. L'ophtalmo-réaction positive des cas avancés parait s'observer alors que les lésions sont déja assez anciennes d'assez vieille date sans que cependant l'organisme soit épuisé et alors qu'il dispose encore des moyens de lutter contre l'infection. Mes constatations à ce point de vue là, sont en grande partie concordantes avec celles de Wolff-Eisner et opposées à celles de Roepke. Elles se rapprochent aussi de celles publiées récemment par Fabier et Knopf.[2] J'ai observé en effet les réactions les plus intenses chez les malades au IIIème degré qui se sont améliorés d'une façon notable au cours de leur traitement.

Je citera à cet égard l'exemple des quelques uns de ces malades. C'est ainsi que la réaction a été très prononcée chez un malade qui après 237 jours de traitement a gagné 10 kilos, de même que chez un certain nombre d'autres malades: un malade qui après 104 jours a gagné 9 kilos, un autre qui après 48 jours a gagné 2 kilos, un troisième qui après 176 jours a gagné 16 kilos, un quatrième qui après 152 jours a gagné 8 kilos ½, un cinquième qui après 148 jours a gagné 3 kilos, un sixième qui après 385 jours a gagné 7 kilos, un

septième qui après 254 jours a gagné 7 kilos, un huitième qui après jours 189 jours a gagné 5 kilos ½, un neuvième qui après 359 jours a gagné 7 kilos, un dixième qui après 131 jours a gagné 9 kilos, un onzième qui après 277 jours a gagné 6 kilos, un douzième qui après 217 jours a gagné 2 kilos, un treizième qui après 191 jours a gagné 2 kilos ½, un quatorzième qui après 109 jours a gagné 22 kilos, etc.

Si l'on analyse d'autre part les cas à lésions avancées ayant presenté une ophtalmo-réaction négative – 33 parmi mes malades—l'on peut constater que la plupart d'entre eux présentaient des lésions tellement avancées qu'ils ont succombé peu de temps après leur entrée à l'hôpital et que chez les autres le pronostic était également tout aussi défavorable.

Point important à signaler: des malades qui à leur entrée à l'hôpital ont eu l'ophtalmo-réaction négative, ont présenté plus tard, alors que leur état s'était amélioré d'une façon notable, une réaction positive. Je peux citer à cet égard l'observation de cinq de mes malades, chez lesquels ce phénomène a été tout a fait net. J'ajoute pour être compter que l'ophtalmo-réaction a été faite la seconde fois dans l'autre oeil pour éviter les phénomènes de sensibilisation signalés par quelques auteurs même chez des personnes en parfait état de santé. J'ai pu constater d'autre part le phénomène inverse: l'ophtalmo réaction positive d'abord, négative ensuite alors que l'état du malade s'était aggravé ou qu'il s'était produit une complication intercurrente.

Quant à la cuti-réaction je l'ai etudiée chez 67 de mes malades. Elle a été positive dans tous les cas sauf chez 9 de ces malades. J'ai employé pour faire la réaction la tuberculine de Koch en solution à 25% et pour la scarification je me suis servi du petit instrument recommandé per Pirquet (impfbohrer). Wolff-Eisner attribue aux différentes modalités de la cuti-réaction une valeur pronostique assez grande. Mes résultats confirment en grande partie, l'opinion de Wolff-Eisner. Dans un premier groupe des faits, la réaction se produit 4–6 heures après la scarification atteint son maximum 20–24 heures après, se maintient sans grand changement le second jour, et disparait après 3–4 jours. Cette façon de réagir après l'application cutanée de la tuberculine s'observe dans les cas au début et dans ceux au Ier et IIème degré ayant un pronostic favorable. Un autre type de réaction est la réaction de très courte durée. Elle commence d'habitude 6 heures après la scarification, atteint très rapidement son point culminant, après 10 heures déja, et ne s'observe plus au courant de deuxième jour. La réaction est tellement insignificante que si l'on ne l'observe pas avec attention elle peut passer complètement inapperçu. Ce type de réaction se produit chez les malades à lésions très avancées. J'ai pu le constater chez 7 de mes malades. L'absence complète de la cuti-réaction aurait comme signification un pronostic absolument défavorable. J'ai pu la constater chez 3 de mes malades chez lesquels l'évolution de la maladie a été tout à fait défavorable. La cuti-réaction tardive et durable

impliquerait un pronostic très favorable. Dans ce type de réaction, le phénomène se produit plus tardivement, le deuxième ou le troisième jour. La réaction conserve ses caractères pendant un temps prolongé, 5–6 jours ou même d'avantage: 2–3 semaines. Chez des malades avancés tels que ceux recu à Filaret ce type de la cuti-réaction n'a pas être observé. Je l'ai constaté cependant d'une façon très nette chez quelques uns des membres du personnel de l'hôpital; l'interne et l'externe du service, le garçon du laboratoire qui manifeste les crachats, etc.

Tels sont les faits que j'ai pu observer relativement à la valeur pronostique de l'ophtalmo- et de la cuti-réaction. Il semble d'après les observations que je viens énoncer qu'on peut accorder une certaine valeur pronostique à ces deux réactions. Il est vrai que cette valeur pronostique n'est que limitée puisque dans ma statistique 70% des malades au IIIème degré ont presenté une réaction positive et cela dès la première instillation de la tuberculine dans l'oeil du malade. Une analyse détaillée de la façon dont cette réaction se produit permet cependant de tirer quelques renseignements sur l'évolution probable de l'infection. Mes conclusions peuvent donc se formuler de la façon suivante:

I. L'ophtalmo-réaction et la cuti-réaction ont été positives dans 68.2% d'un grand nombre des cas à lésions avancées que j'ai pu suivre jusqu'à ce moment (123 cas observés).

II. Ces réactions ont été négatives chez des malades dont le pronostic a été complètement défavorable.

III. Les malades ayant eu d'abord une réaction négative peuvent présenter une réaction positive dans le cas où une amélioration notable se produit dans leur état. Le phénomène inverse peut s'observer: la réaction qui avait été d'abord positive devient négative si la maladie prend une tournure grave ou s'il se produit une complication intercurrente (pneumothorax, méningite tuberculeuse, généralisation).

BIBLIOGRAPHY.

1. Roepke: Beiträge zur Klinik der Tuberkulose, Bd. ix, Heft 3.
2. Fabier et Knopf: Berliner klinische Wochenschrift, August, 1908.

THE AGGLUTINATING POWER IN TUBERCULOUS PATIENTS. – SERUM DIAGNOSIS.—SERUM PROGNOSIS.

By Professor Paul Courmont,

of the University of Lyon.

The serum diagnosis of tuberculosis is actually one of the most employed and most certain laboratory methods of diagnosis in tuberculosis. It is practised like that of typhoid fever, by mixing the serum of the patient with a certain quantity of liquid homogeneous culture of the bacillus of tuberculosis.

I. Historical.

It is known that the usual culture of the bacillus of Koch cannot be utilized for agglutination.

It was M. Arloing who, in 1898,[1] having obtained a fluid homogeneous culture of the bacillus of Koch and its agglutination by the serum of tuberculous human beings or animals, created thus the serodiagnosis of tuberculosis.

Messrs. Arloing and Paul Courmont[2] then perfected the method, determined the best manner of cultivating the homogeneous cultures, applied the serodiagnosis to hundreds of patients and studied on these, and on animals rendered tuberculous, the agglutinating power of the blood.

M. Paul Courmont has studied[6] local serodiagnosis (diagnosis of the nature of the pathological serous fluids by the agglutinating power of these effusions) and the seroprognosis of pleurisies. The Lyonese method is employed almost everywhere; the works on this question are very numerous; we may cite among the authors who have approved us:

In Paris: Widal and Ravaut; Dieulafoy; Schrapf; Sabareanu and Salomon, pupils of Prof. Landouzy; in Bordeaux: Ferre, Mongour, and Buard; in Lille: Carriere; in Marseilles: Hawthorn; in Montpelier: Lagriffoul; in Geneva: Bard and Humbert; in Germany: Bendix, Rumpf and Guinard, Romberg: in Russia: Kazarinow, Skakarin; in Italy: Marzagalli, Caffareno, Marchetti and Stefanelli, Marini; in Rumania: Thomescu and Gracosky, etc.

If some authors, on the contrary, have contested the importance and value of the serodiagnosis, this arises from their not having avoided the following causes of error:

II. Causes of Error to be Avoided.

1. Techinic.—First, one must possess a good agglutinable bacillus; we have shown that the agglutinability does not belong to all the bacilli of Koch.[7] Our bacillus A (human tuberculosis—Arloing) fulfils all the conditions of facility of culture and agglutinability. It is the one which we sent to all those who asked us for the same, and most of the results obtained in different parts of the world were obtained with this bacillus.

Then one must obtain and employ a liquid homogeneous culture in the conditions which we have exposed lengthily elsewhere: cultures four to eight weeks old, diluted with salt water at 7 per cent., tested with the standard serum, mixed with serum in suitable proportion, it being necessary to take into account only those reactions visible to the naked eye.

These conditions are quite easy to follow in a well-appointed laboratory; we can, moreover, provide tubes of homogeneous cultures ready to be employed, just as one provides tuberculin dry or liquid for tuberculin reactions. On the other hand, it is evident that technical modifications in the preparation of the cultures, in their age, their dilution, etc., modify their agglutinability and prevent one from comparing the results thus obtained with those obtained by ourselves and by all those who have followed our instructions.

2. Appreciation and Value of the Degree of Agglutination.—We have said that for the serum of an adult man one mixed the serum and the culture in three little tubes in the following proportions: (1) One part of serum to five of culture; (2) 1 to 10; (3) 1 to 15. In these conditions the serum of a man free from all evident or latent tuberculosis would not agglutinate ordinarily at 1 to 5, whereas the serum of the tuberculous will agglutinate at a degree varying between 1 to 5 and 1 to 15 or 20, and rarely at a higher degree.

But if one changes the conditions one gets quite different results: for instance, if one employs cultures which are not agglutinable, one would have only negative results; if, on the contrary, one employs cultures which are too agglutinable, one obtains with the same serum much higher degrees of agglutination, and these can no longer be compared to ours. This is what happened to Kinghorn, for example, who found much more elevated agglutinations than we did.

One knows that every serum, even normal, possesses a certain natural agglutinous power; the specificity of the agglutinating reaction is only relative—quantitative and not qualitative. It is only from a certain degree that

the agglutinating reaction vis-à-vis of a bacillus has a specific and diagnostic importance, and this degree varies according to the different animal species. For instance, the serum of a healthy dog can agglutinate our dilution of homogeneous culture in the proportion of 1 to 30; the serum of an adult cow, non-tuberculous, would agglutinate it ordinarily at 1 to 5. Moreover, the serum of an animal species agglutinates at different degrees according to the age. M. Arloing has shown that serum of the calf does not agglutinate at 1 to 5, whereas the serum of a healthy cow does agglutinate in this degree.

Consequently, for a given animal species the agglutination of a bacillus would only be specific above the ordinary degree of agglutination of the normal serum of this species for this bacillus; moreover, the age must likewise be taken into consideration. To summarize: A serum agglutination has diagnostic value for a given subject only according as it surpasses the agglutinating power of the serum of normal subjects of the same species and the same age.

For human beings it is not easy to fix this limit, for it is always difficult to prove that the subject is healthy and has not a latent tuberculous lesion. Nevertheless, for an adult subject, in the exact conditions of our technic, the limit of the pathological agglutination seems to commence at 1 to 5. We will see further on that this limit is lowered in children. But it is evident that if one employs cultures which are much more agglutinable than ours, this limit must be raised above 1 to 5, because in this condition the normal agglutinating power of the serum of healthy subjects would surpass this limit; one must then only consider as specific much more intense serum-reactions.

It is certainly through not having taken these rules into account that some authors, and especially Kinghorn, have considered as specific certain sero-reactions due to the normal agglutinating power, and have found as many positive reactions in healthy people as in those who are tuberculous. Kinghorn finds, in fact, many reactions at 1 to 75 and 1 to 100, degrees which we hardly ever obtain in a tuberculous man. Consequently, his cultures are much more agglutinable than ours, so that the normal human serum which for us agglutinates only below 1 to 5, agglutinates for Kinghorn above this degree, and is considered by him like a given specific reaction.

3. Clinical Interpretation.—One must take care not to take the seroreaction for an infallible sign, promising a diagnosis of mathematical precision.

Like every pathological sign, like the ophthalmo-reaction or the injection of tuberculin, this reaction must be interpreted and discussed comparatively with the other symptoms furnished by the study of the case. The sero-diagnosis only takes its full value in cases where the clinical examination has already been made "in the case of a suspected subject," as we wrote already

in 1898 with M. Arloing. Applied to healthy subjects, non-suspects of tuberculosis, it has only slight value by itself.

One must remember also that the general serodiagnosis (with the blood-serum) does not give the diagnosis of the localization of the lesions, but only that of general tuberculosis; it is for the clinician to apply to a local lesion the results of the serodiagnosis.

We repeat that all these precautions apply not only to the serum diagnosis, but to all the methods based on the employment of the tuberculin (cutaneous injection, ophthalmo-reaction), which are, moreover, liable to many other reproaches.

III. Proofs of the Value of the Serodiagnosis.

The best proofs are the good practical results which the serodiagnosis has given to a great number of authors. But there are two kinds of specially conclusive proofs:

1. Statistics Among the Bovines.—In cows one can have statistics in which the autopsies control the serum reaction. Under these conditions M. Arloing has seen that the serodiagnosis is always negative when the cow is non-tuberculous, and positive 98 per cent. when there are tuberculous lesions.[8]

2. Statistics with Pleurisies in Man.—For human pleurisies one can have the certitude of the tuberculous (or not) nature of the malady (by the clinic, through inoculation and cytology combined). In such conditions, in a statistic of 112 cases, we have never had a positive reaction with the pleural liquid when the pleurisy was not tuberculous; on the contrary, we had 76 per cent. of positive reactions when the pleurisy was tuberculous.[6]

If the results of the serum agglutination with the blood-serum of human beings (tuberculous or not) are in appearance less easy to interpret, this depends on the variations of the agglutinating power according to the form, the gravity, the cure or curability of the lesions, according to the age of the subject, which we summarize as follows:

IV. The Agglutinative Reaction in Practice (Serodiagnosis).

According to our own personal statistics, covering more than 1200 cases, we have obtained positive seroreactions:

1. In tuberculous patients (90 per cent.).
2. In hospital cases apparently not tuberculous (40 per cent.).
3. In apparently healthy subjects (30 per cent.).

1. In the Tuberculous.—The agglutination varies in frequency and in intensity according to the following conditions:

(*a*) *The Localization of the Lesions.*—Localized tuberculosis (called

"surgical")[8] are often less agglutinating (75 per cent. in the cases of tuberculosis of bone, of skin, of lupus).[9] The cases of tuberculosis of viscera, of lung, of pleural and other serous membranes, of intestine, are those which agglutinate the most.

(*b*) *The Gravity of the Lesions.*—Those are the most serious tuberculosis cases with wide-spread lesions, rapid consumption, which give nearly all the negative seroreactions (consumptive subjects attacked by tuberculous pneumonia, meningitis, granulie). Conversely, curable cases, such as fibrous tuberculosis, give the largest proportion of positive reactions (pleurisy à frigore, fibrous pulmonary tuberculosis, chronic bronchitis, or emphyseme with slight tuberculous lesions, curable adenitis, etc.).

It is the same with animals experimentally tuberculous.[10] Two conclusions result from this. From the point of view of the serodiagnosis this will not give such good results in the grave and rapid forms, but it will show latent cases which work slowly and are curable—that is, in those cases where the diagnosis is both most difficult and most useful.

As to the seroprognosis, we shall speak later.

(*c*) *The Curing of the Lesions.*—Tuberculoses which are on the way to being cured agglutinate very well. One must know, therefore, that the agglutinating power of the blood persists long after the anatomical cure of the lesions. Consequently, the serum agglutination can make a retrospective diagnosis of a cured tuberculosis, for instance, of a past adenitis or pleurisy.

On the other hand, one must always remember the possibility of such a case when one interprets the seroreaction in a subject who has clinically no sign of tuberculosis: the reaction might be due to the persistent power of agglutination remaining in the blood after the cure of an old tuberculosis which has been cured without leaving any trace.

This difficulty, moreover, is not inherent to the serodiagnosis only; we have seen the ophthalmo-reaction positive in old subjects, whereas the autopsy and inoculation of the organs showed no trace of tuberculosis in evolution nor the presence of any bacilli of Koch.

This merely shows that the laboratory proceedings of diagnosis must be discussed in each particular case with the help of the clinical observation.

(*d*) *The Age.*[11]—The serum of the newly born does not agglutinate (Romberg, Descos); that of tuberculous children agglutinates, but generally less than that of adults: this degree of agglutinating power rises with the age of the children. It results that the serum reaction has a positive significance in children at a lower degree of agglutination than in adults; this is very important for its practical application. (See the thesis of Descos.) It is in adults that the seroreaction presents the maximum of frequency and intensity.

In the aged[4] one finds many weak seroreactions caused by old tuberculous lesions, more or less healed; but the strong seroreactions are important in showing an old tuberculosis not yet completely extinct. It is very important to know these variations according to age for practical application, *i. e.*, for the theoretical question of latent tuberculosis.

One same degree of agglutination has not the same importance at different ages.

On the other hand, the results of serum diagnosis at different ages agree absolutely with those of anatomical-pathological statistics of Naegeli, of Germany.

2. By the Patients Apparently not Tuberculous.—In these cases the seroreaction is positive in 35 to 40 per cent.; this is not astonishing, taking in consideration the great frequency of tuberculosis, more or less latent, in hospital patients. With tuberculin one arrives at analogous results. Beck observed in Berlin 46 per cent. positive tuberculin reactions in 2000 patients who were apparently not tuberculous.

Acute infections do not give generally to the serum the agglutinating power for the bacillus of Koch. One must, however, classify separately typhoid fever, for 75 per cent. of the typhoid patients agglutinate the bacilli of Koch, just as if they were tuberculous, whereas the autopsy may not show any tuberculous lesions.

But from a theoretical point of view our experiments with M. Arloing in men and animals show that there is no relation between the agglutinating power of serum on the typhoid bacilli and the tuberculous bacilli. It seems that it is not the same agglutinin which acts on the two bacilli, but two distinct kinds of agglutinins. The cause of this double agglutinating power of the typhoid serum is still obscure. It is perhaps due to the accidental invasion of the Koch bacilli through the intestinal ulcerations, or to a sort of displacement of the Koch bacilli latent in the organism. At any rate, this prevents the application of the tuberculous seroreaction to distinguish between typhoid fever and tuberculosis. The serodiagnosis of tuberculosis has less value in the acute forms than in the torpid and chronic forms. The same inconvenience exists with the tuberculin reaction which cannot be applied to fever cases, and with the ophthalmo-reaction, which is positive in most cases of typhoid fever without coexistence of tuberculosis.[12]

3. By Subjects Healthy in Appearance.—The seroreaction is positive in about 30 per cent. It discovers also cases of latent tuberculosis, no matter how slight this may be. But as many cases of latent and slight tuberculosis are compatible with very good health, the seroreaction in such cases has only the value of a "reaction d'attente" (expectant reaction); alone and without other symptoms the seroreaction has no practical importance, for instance, in soldiers. We may observe, furthermore, that the results with tuberculin

confirm those of the serum diagnosis in healthy subjects. (See the statistics of Beck.)

V. Comparison of the Serodiagnosis and the Tuberculin Reactions—Advantages of the Seroreaction.

If one compares the results given by the serodiagnosis and the tuberculin reactions (subcutaneous injections or ophthalmo-reaction), one sees that these methods give similar results, but many advantages are in favor of the serodiagnosis. With these three methods the results are positive in most cases of active tuberculosis, the cases which give no reactions being often the gravest; for instance, in advanced consumption.

With these three methods the results are positive in a fairly large number of cases in which neither the clinical examination, not even sometimes the autopsy, can discover tuberculosis. The accordance of the results proves that there is latent tuberculosis with very slight lesions often compatible with good health, and which can be discovered only by this very delicate laboratory method.

It is extremely remarkable that injection of tuberculin and serodiagnosis give about the same percentage of positive reactions in patients who are not evidently tuberculous (40 per cent. with the serodiagnosis and 46 per cent. with the tuberculin, according to Beck). It is also curious to see that the ophthalmo-reaction is positive in typhoid cases, just as the seroreaction.

At any rate, the few objections which one can make to the serodiagnosis (causes of error in feverish cases and in typhoid fever, and too great sensitiveness of the method, which discovers the slightest tuberculous infections, even those compatible with health) concern equally the injection of tuberculin and the ophthalmo-reaction, as we have explained above.

The particular great advantages of the serodiagnosis are the following:

1. *Absolute harmlessness*, since the taking of a little blood cannot give rise to accidents or inconveniences sometimes attributed, with reason, to the tuberculin and ophthalmo-reactions.

2. *Facility of application*, since a few drops of blood suffice, and it is needless to observe the patients during several days, as in the two other methods.

3. *Importance of the variations of the agglutinating power.* Given the harmlessness and facility of application, one can repeat the reaction as often as one likes, and the variations of the agglutinating power are of great importance, not only for the diagnosis, but also for the prognosis.

4. *Application of local serum-diagnosis*, which is impossible with other methods.

VI. Local Serodiagnosis.

The seroreaction is generally made with blood-serum; in this case it only gives a general serodiagnosis, simply proving the general specific impregna-

tion of the blood with a given infection, no matter where the lesions may be. But we have established, since 1908, the possibility and the good results of a local serodiagnosis.[6] This is made with local effusions of the serous membranes, for instance, in the pleurisies. We have established that when a serous membrane is infected by tuberculosis, a local reaction is produced, and agglutinins are formed locally, independently of what happens in the blood. The search of the seroreaction with the pleural fluid furnishes the proof of the local tuberculosis. Our numerous works on the subject (more than 200 cases of effusions, of which 115 were tuberculous pleurisies) have been confirmed by Mongour and Buard, Widal and Ravaut, Dieulafoy, Landouzy, Sabareanu, and Salomon, Hawthorn, in France; Bendix in Germany; Kazarinow, in Russia; Marini, Marchetti, and Stefanelli in Italy,[18] and other authors, whose statistics are absolutely similar to ours. The most conclusive results are given by the pleural fluids. The fluid of tuberculous pleurisies agglutinates (at least at 1 to 5) in 76 per cent. of adults (statistics of 115 cases). Negative cases, although tuberculous, concern always graver forms. The non-tuberculous fluids are not agglutinous, even at 1 to 5 (with the exception of two or three doubtful cases).

The agglutinating power of the tuberculous fluids is ordinarily less elevated than that of the blood-serum; but it may be sometimes more elevated, or can exist only in the pleuritic fluid and not in the blood. It would, therefore, seem that the pleural membrane can produce *in loco* agglutinative substance.

In Practice.—1. Positive seroreaction (at 1 to 5 and above) is a sign of great value in favor of the tuberculous nature of pleurisies. The minute comparison of the serodiagnosis with the cytology and the results of inoculation of fluid in the guinea-pig prove the absolute accordance of the three methods. The serodiagnosis has the advantage of greater facility and rapidity; one does not need the presence of the patient, a few drops of liquid suffice, and one can transport easily this little quantity of fluid for examination.

2. Negative reaction only constitutes a presumption against the diagnosis of tuberculosis. One must in this case repeat the experiment.

3. The comparison of the agglutinating power of the blood with that of pleural fluid would give interesting results.

One can apply the same conclusions to the diagnosis of other pathological fluids (especially ascites and hydrarthroses), except to meningitis, of which the fluid is never agglutinative.

VII. Seroprognosis.

The general idea of the seroprognosis in sickness, and the signification of the agglutinating reaction in the evolution of the infectious diseases, was advanced by us for the first time in 1896–97, apropos of typhoid fever.[13] We have established that the degree of the agglutinating power of the blood

is the more intense if the infection is less grave and the resistance of the subject is greater. For tuberculosis the question is more complicated, on account of the variability of the forms and the duration of the illness. But it would be as important as it is difficult to establish this prognosis of the illness by the varying agglutinating power in tuberculous patients. Since this date we have said: "The agglutinating power seems to be inverse to the gravity of the infection"; and in 1900 we arrived at the same conclusions in animals made experimentally tuberculous.[2]

The arguments on which the seroprognosis is based are:

1. *General Statistics.*—The tuberculous, of whom the serum is not agglutinating (10 per cent. to 15 per cent.) are nearly all very seriously ill; the subjects who have advanced consumption, miliary tuberculosis, and caseous pneumonia, meningitis, have nearly all a negative seroreaction.

2. *Experiments in Animals made Experimentally Tuberculous.*—The development of the agglutinating power is the more elevated when the tuberculosis is less virulent and the animal more resistant, and conversely.[10]

3. *Variations of Intensity of the Agglutinating Power of the Tuberculous.*—These variations appear to be dependent upon the prognosis of the disease. Very elevated reactions are found especially in subjects in whom the tuberculosis is slight or on the way to healing (local tuberculosis of the viscera, fibrous tuberculosis of the lungs, primitive pleural tuberculosis of Landouzy, etc.). Reciprocally, weak agglutinations are found especially in patients more seriously ill.

4. *Variations of the Agglutinating Power in the Same Subject.*—If one observes at length the same tuberculous subject, one sees frequently the agglutinating power of his serum elevating itself if the patient heals, and, on the contrary, lowers itself if the disease gets worse, and at times even disappears completely. Here are some examples of these two cases:

(*a*) *Pleurotuberculosis with favorable seroprognosis:* Guisep, eighteen years; has serofibrous benign pleurisy, without complications, and will be absolutely cured.

Agglutinating power of pleuritic fluid:

Ninth day	+ 5
Fourteenth day	+ 10
Twenty-first day	+ 15

(*b*) Tuberculosis with unfavorable seroprognosis; M., twenty-eight years; pregnant; double pleurisy with fever, secondary galloping phthisis; death in ninety-six days.

AGGLUTINATING POWER

Of Blood.		Of Pleuritic Fluid.	
Twentieth day	+ 10		+ 5
Fiftieth day	5		0
Eightieth day	0		0
Ninety-fifth day	0		0

In the first case one sees the agglutinating power growing until recovery, and in the second decreasing until death.

5. *Mortality Through Pleurisy According to the Agglutinating Power of the Pleural Fluids.*—We have studied more than 120 cases of tuberculous pleurisies and followed the patients during eight years. If one compares the mortality of patients in whom the pleural fluids were agglutinous to that of patients of whom the fluid was not agglutinous, one arrives at the following conclusions:

75 per cent. of cures in cases of positive reaction.

73 per cent. of death in cases of negative reaction.

This fact is a new proof that the agglutinating power is a protective reaction, or at least an index of the protective reaction.

In America, Ravenel[15] and Landis[16] arrive at the same conclusions. Eight years ago Bendix,[17] in Germany, wrote also in favor of the seroprognosis.

Conclusions.

1. The agglutinating power of the humoral liquids in tuberculous patients is an important symptom of tubercular infection. It must be studied in all its variations, according to the age of the patients, to localization, form, and degree of lesions, and also in relation to other symptoms of infection on protective reactions in every case.

2. In order to make a valuable investigation, seroreaction must be looked for under indispensable technical conditions as regards the choice of the culture, its method, and the technicalities of the reaction.

3. Given the first, that the agglutinating power of normal serum varies according to age and also to the animal species investigated, seroreaction has value only when the degree of agglutination is higher than the ordinary degree of agglutinating power of the serum of normal individuals of the same age and belonging to the same species.

4. *Serodiagnosis.*—For practical purposes seroreaction must be applied with great clinical discrimination; its results must be compared with the other symptoms. It would not be wise to regard as clinically tuberculous a patient for the sole reason that his serum agglutinates Koch's bacilli. The reaction can have no diagnostic value unless there are reasons justifying the suspicion of tuberculosis. Positive seroreaction has a great value: negative reaction is of less value. Diagnostically, seroreaction can be considered from two different points of view:

A. *General Reaction* (*With Blood-serum*).—It does not give information as regards the location of the lesions, and indicates only that the system has been or is actually under the influence of tuberculosis. The serodiagnosis will be of quite special use in children, in old people, and also adults suffer-

ing from chronic, torpid, or latent forms of tuberculosis. Figures pointing to the frequency of latent tuberculosis in adults who clinically do not appear tuberculous are almost the same with seroreaction as with tuberculin test (either subcutaneously or in the eye).

B. *Local Seroreaction.*—It consists in testing agglutinating power of serous effusions and indicates the location of the lesions. It is particularly useful for the diagnosis of tuberculous pleurisy, and its results are in accordance with such as are given by inoculations or cytodiagnosis.

5. *Nature and Prognostical Value of Seroreaction in Tuberculous Patients—Seroprognosis.*—As is the case in many other diseases, the agglutinating power of blood-serum and other organic liquids in tuberculosis is proportional to the resisting power of the patients; furthermore, it is in an inverse ratio with the virulence of infection. Seroreaction is absent, especially in very serious or very advanced cases of tuberculosis. It reaches its maximum height in cases which are in the process of healing. It can diminish or disappear sometimes before death; it can, on the contrary, increase when there is an improvement pointing toward healing or an arrest. It seems to be an index of the protective reaction of the system.

Practically, a study of seroreaction and its variation may be of some prognostic value. In tubercular pleural effusions, an increasing agglutinating power carries a good prognosis, and, especially, failing any reaction, one must be prepared for a sooner or later fatal evolution.

PRINCIPALES REFERENCES.

1. S. Arloing: "Sur l'obtention de cultures homogènes du bacille de la tuberculose," C. rendus Acad. des Sciences, Paris, May 9, 1898. "Agglutination du b. de Koch par le serum sanguin des tuberculeux," Congres de médecine Montpellier, 1898.
2. S. Arloing et Paul Courmont: "De l'obtention des cultures homogènes les plus propices a l'etude du phénomène de l'agglutination par le sérum sanguin des tuberculeux," Academie des Sciences, Paris, 3 Aout, 19 Septembre, 1898. "Recherche et valeur clinique de l'agglutination du b. de Koch," Acad. des Sciences, Paris, 19 Septembre, 1898. Congres de la tuberculose, Paris, 1898. "Séro-diagnostic de la Tuberculose," Congres Tuberculose, Berlin, 1899. Zeitschrift für Tuberkulose, 1900, B. I., H. I., Gazette des hôpitaux, Paris, 1 Decembre, 1900.
3. Paul Courmont: "Le Sero-diagnostic des tuberculoses dites chirurgicules," Theside Clenient, Lyons, 1900.
4. Paul Courmont: "Le Séro-diagnostic de la tuberculose chez le vieillard," Bulletin Société medicale des hôpit. de Lyons, 22 Mars, 1904.
5. Paul Courmont: "Tuberculose latente et séro-diagnostic," Bulletin Société medicale des hôpit. de Lyons, 22 Mars, 1904.
6. Paul Courmont: "Séro-diagnostic des epanchement tuberculeux," Congres de la tuberculose, Paris, 1898. "L'agglutination du b. de Koch par les epanchement tuberculeux," Societe de Biologie, November, 1900. Archiv de médecine expérimentale, Novembre, 1900.
7. S. Arloing et Paul Courmont: "Variations de l'agglutinabilite des bacilles de la tuberculose. Deux memoires," Revue de la Tubereulose, Juni et Octobre, 1904.
8. S. Arloing: Journal de médecine veterinaire de Lyon, Septembre, 1900.
9. Paul Courmont et Nicolas: "Séro-diagnostic tuberculeux chez les lupiques," Société medicale des hôpit. de Lyons, Novembre, 1907.

10. S. Arloing et P. Courmont: "Des causes qui modifient le pouvoir agglutinierent sujets expérimentalement tuberculeux," Journal de physiol. et pathol. générale, No. 1, 1900.
11. Descos: "La séro-diagnostic de la tuberculose chez les enfants," These, Lyons, 1902.
12. F. Arloing: "Ophthalmo-reaction," Journal de physiol. et pathol. generale, 1908.
13. Paul Courmont: "Signification de la reaction agglutinante chez les typhiques," These de Lyon, 1897, Société de Biologie, 1897–98.
14. P. Courmont: "Séro-pronostic des pleurésies tuberculeuses," Jour. Amer. Med. Assoc., May 14, 1906.
15. Ravenel et Landis: "Agglutination Studies in Tuberculosis," The Medical News, 1907.
16. Landis: "Studies in Agglutination in Tuberculosis," Journal of Medical Research, 1908.
17. Bendix: "Zur Séro-Diagnose der Tuberculose," Deutsche med. Wochen., April, 1900.
18. Mongeur et Buard: Soc. de Biologie, 1899.

Bronstein: Soc. de pédiatrie de Moscow, Wratch, 1901.
Dieulafoy: Semaine médicale, 1903, et Cliniques medicales de l'Hôtel-Dieu.
Widal et Ravant: "Agglutination du b. de Koch dans 24 cas de pleureses la tuberculose," Congrès de Lyon, 1908.
Froment: "Séro-diagnostic de la tuberculose chez le vieillard," Soc. de Biologie, 1903.
Hawthorn: Séro-reaction tuberculeuse, Soc. de Biologie, 1903. Journal de physiol. et pathol. générale, 1903.
Rodet et Largrifoul: Journal de physiol. et pathol. générale, No. 8, 1902.
Rumpfet et Guinard: "Recherches sur la séro-réaction tuberculeuse," Presse medicale, Mars, 1902. Deutsche med. Woch., No. 8, 1902.
Kazarinov: "Contribution a l'étude du séro-diagnostic tuberculeux," Nevrologent-cheski, 849–897, 1901.
Il Vento: "Sull agglutinabilite del bacille tubercular et suo importanza diagnostica," Riforma medica, No. 261, 266, 1902.
Marzagalli et Caffareno: Twelfth Congress of Medicine Italian, Rome, 1902.
Marchetti et Stefanelli: "Sullo séro-reazione tuberculose," Rivista critica di medica clinica, 31 Octobre, No. 42, 43, 44, 1903.
Largriffoul et Pagès: Société Biologie, 29 Juillet, 1903.
J. Teissier: "Valeur pronostique de la séro-reaction," Congrès italien de medecine interne, Génes, 1905, p. 920.
P. Courmont: "Valeur sémiologique de la réaction agglutinante chez les tuberculeux," Congres de Lyon de l'Association française l'Avancement des Sciences, Lyon, 1906.
S. Arloing, Bayle et Dumarest: "Étude sur les rapports entre la sero-agglutination et l'evolution de la tuberculose chez l'homme," Congrès de la Tuberculose, Paris, 1905.

ON THE CONJUNCTIVAL TUBERCULIN REACTION.

By V. Malmström,

Stockholm.

At the request of Dr. M. Bruhn-Fahraeus, chief physician at Sabbatsberg, I have examined the conjunctival reactions on 252 patients at the Sabbatsberg hospital. An account is given in the following pages of a suitable way of carrying out the experiments, and also of the course and the diagnostic value of the reaction.

Most of the examinations of which accounts have hitherto been published have been carried out either with dry glycerin-free tuberculin, according to Calmette's method, with a 1 or ½ per cent. solution, or else with the usual Alttuberculin in a 1–2–4 per cent. solution.

Many writers, ophthalmologists especially, have observed serious consequences of tuberculin instillation in the form of intensely purulent and hemorrhagic conjunctivitis, phlyctenular ulcerations of the cornea, etc. (Kleinberger,[1] Lapersone,[2] Adam,[3] Collin[4]), and therefore insist on the necessity of caution in the use of the method. There have been, especially, some unpleasant experiences of the results of the repeated instillations in the same eye, a method employed by a number of investigators.

I have tried several different solutions, viz., the dry, glycerin-free tuberculin test from the firm of Poulenc frères, of a strength of 1:100, 1:250, and 1:500, and ordinary Alttuberculin from Farbwerke Höchst-am-Main, in 1 per cent. and ½ per cent. solutions. All these solutions, with the exception of the last named, have in some cases produced unduly violent reactions: conjunctivitis of long duration, which has made therapeutical interference necessary; phlyctenules; purulent conjunctivitis with edema of the eyelid. On account of these experiences, together with the above-mentioned reports from other investigators, I have used ½ per cent. Höchst's Alttuberculin in most experiments, and do not consider it advisable to recommend the use of stronger solutions. Two hundred patients have been treated with the solution just named, the greater number of them twice, care being taken never to use the same eye for both instillations. None of these patients has experienced any unpleasant results worth mentioning. In one case, where a second instillation in the same eye had been tried, and also in another instance where, in consequence of some indiscretion, several drops

had been instilled at once into the same eye, the weak solution, too, caused unpleasant results.

The solutions have been renewed every fifth or sixth day, aseptic precautions being carefully observed. With the exception of the very first experiments, the reactions have been carried out on perfectly healthy eyes only.

Among the observations made respecting the course of the reaction, the following are here recorded:

Case 1.—E. M. D., sixteen years of age. Diagnosis: Tuberculosis laryngis, glandular, lymph, colli et bronchial.

On November 7, 1907, there was given one drop tuberculin test 1:100 in the left conjunctival sac. Eight hours later intense conjunctivitis with fibrinous purulent exudation was observed; on the following day there was also observed some slight chemosis, a greenish discoloration of the iris, which retained its markings and brilliancy, and a dilatation of the pupil. On the third and to the fifth day the temperature rose to a maximum of 37.9° C. (100.2° F.). On the eleventh and twelfth days after the instillation there was again a rise of temperature to, respectively, 37.8° and 38.6° C. (100° and 101.48° F.), besides which the lymphoma on the neck showed acute swelling and tenderness and miliary phlyctenules appeared on the limbus corneæ. During a period of three weeks before and six weeks after the carrying-out of the conjunctival experiment the patient's temperature never exceeded 37.4° C. (99.32° F.).

Case 2.—G. L., eighteen years of age. Diagnosis: Rheumatism, musc. et artic. subac.

In 1904 the patient had been treated for tbc., apic. pulm. dx. Examination of the lungs now gives lengthened expiration in the right fossa supraclavicularis and infraclavicularis; otherwise nothing abnormal. In the tables the patient is included in the number of suspected cases.

On November 8th conjunctival reaction was made with tuberculin test 1 : 100, with negative result as far as the conjunctiva was concerned. On November 11th the evening temperature rose to 38.2° C. (100.76° F.) without any apparent local cause. On November 14th the patient was again without fever. The patient was without fever during the whole period of residence at the hospital (November 2d to December 19th), except when subcutaneous tuberculin experiments were carried out later on, which caused a rise of temperature to a maximum of 37.7° C. (99.86° F.), but without typical positive result. On December 4th fresh instillation of the same tuberculin solution was made in the other eye, without causing any fever or reaction in the conjunctiva.

Case 3.—A. D. T., fifteen years of age. Diagnosis: Tuberculosis pulm.

On November 20th one drop of tuberculin test 1 : 250 was instilled into the left eye. On the following day the conjunctiva became slightly red and the temperature rose to 37.8° C. (100° F.). On November 28th the experiment was renewed with tuberculin test 1 : 500 in the right eye, whereupon an exceedingly violent reaction showed itself in the conjunctiva, with secretion of pus and swelling of the eyelid. On November 29th the evening temperature was 38.1° C. (100.58° F.). With the exception of these two

rises after the instillations the temperature during the period from September 22d to December 29th did not exceed 37.6° C. (99.68° F.).

In these three cases, in which the patients otherwise always were afebrile, there occurred, twenty-four to seventy-two hours after the instillations, rises of temperature, which soon passed over, and for which no local cause could be ascertained. In Case 3 reactions were made twice with the same patient, and on each occasion the temperature rose. In Case 4 there was nothing conjunctival observed, but only fever.

It thus seems as if the conjunctival reaction could occasion fever, and this in direct opposition to what has been stated in the literature on the subject. As far as I have been able to discover, only Andeoud[5] and Wolff-Eisner[7] have observed a rise of temperature to be a consequence of this experiment. It is worthy of attention that the three patients mentioned above were pretty young people. Case 3 also shows very manifestly the increased sensitiveness to tuberculin which an instillation in the one conjunctival sac produces in the conjunctiva of the other eye, a fact that has been pointed out by Cohn,[6] among others. On the occasion of the second experiment the reaction proved much more violent than on the first occasion, in spite of the fact that the solution employed in the second case was only half so strong as that used in the first.

The following tables illustrate the diagnostic value of the method:

TABLE I.—EXAMINATIONS WITH ½ PER CENT. ALTTUBERCULIN.

	Total Number Examined.	Giving Positive Reaction.	Giving Negative Reaction.
Group I. Certainly cases of tuberculosis . .	71	49 = 69 per cent.	22 = 31 per cent.
" II. Suspected cases of tuberculosis .	49	18 = 37 per cent.	31 = 63 per cent.
" III. Clinically free from tuberculosis.	80	8 = 10 per cent.	72 = 90 per cent.
Total.....	200		

Group I embraces cases of lung tuberculosis, of which 20 per cent. were in the first, 25 per cent. in the second, and 55 per cent. in the third, stage (Turban-Gerhardt D.R. Gesundheitsamt), in addition to cases of laryngeal, osseous, articular, urogenital, and peritoneal tuberculosis.

In this and the following tables all clinically primary pleuritis have been included in Group II.

The greater number of the cases showing negative reaction have, after the lapse of at least four days, been once more examined with tuberculin solution of the same strength, when it was made a rule not to use the same eye that was first employed. The results are given in Table II. All the cases given in this table are included in the class giving negative reaction in Table I.

TABLE II.—RENEWED INVESTIGATION WITH ½ PER CENT. ALTTUBERCULIN.

	Total Number Examined.	Giving Positive Reaction.	Giving Negative Reaction.
Group I. Certainly cases of tuberculosis	16	9 = 56 per cent.	7 = 44 per cent.
" II. Suspected cases of tuberculosis	25	4 = 16 per cent.	21 = 84 per cent.
" III. Clinically free from tuberculosis	12	2 = 5 per cent.	40 = 95 per cent.
Total	83		

It is thus seen that, on the first trial, a number of patients showed negative reaction who, on the second occasion, gave a positive one.

This phenomenon, which has been pointed out before, especially by Cohn,[6] is, according to the table, of rare occurrence among those free from tuberculosis, while it occurs pretty frequently among those suffering from that disease, and it should be possible, therefore, to employ it in the way here described in order to supplement the results of a first investigation. The final figures for the cases giving positive reaction at the first and second examinations together are then:

For Group I	86 per cent.
" " II	47 per cent.
" " III	14 per cent.

It has been already pointed out that it is not without danger that the same eye can be used for both experiments, within a short period, at least. The diagnostic value of repeated instillations in the same eye are, too, very much called into question by Cohn (loc. cit. and Levy[7]).

Of the patients suffering from tuberculosis who showed negative reaction, 2 were cachectical in a high degree and 2 others died—one seven days, the other nine, after the investigation.

Those clinically free from tuberculosis who showed positive reaction have the following diagnosis: 1 fractura femoris, 1 rheumat. art. subac., 4 pneumonia ac., 1 albuminuria cyclica, 1 nephrit. chron., 1 paraplegia, 1 healthy.

The investigations that were made by means of other solutions are given here together in one table.

TABLE III.—EXAMINATIONS WITH TUBERCULIN TEST 1 : 100, 1 : 250, 1 : 500, AND TUBERCULIN HÖCHST, 1 : 100.

	Total Number Examined.	Giving Positive Reaction.	Giving Negative Reaction.
Group I. Certainly cases of tuberculosis	33	30 = 90 per cent.	3 = 10 per cent.
" II. Suspected cases of tuberculosis	5	2 = 40 per cent.	3 = 60 per cent.
" III. Clinically free from tuberculosis	14	1 = 7 per cent.	13 = 93 per cent.
Total	52		

Of the 252 who have been examined, 25 have come to section when, in 20 cases (9 tuberculous, 11 non-tuberculous), the accuracy of the issue of the conjunctival reaction was confirmed. In the 5 other cases, however, where the reaction, carried out one month before death, proved negative, tubercular changes were proved on dissection, one of the cases, judging macroscopically, showing fully healed tuberculosis.

For the sake of comparison, subcutaneous tuberculin injections have been made in 11 of the cases. In 8 cases there is full agreement with the conjunctival reactions (5 positive and 3 negative). In one assured case of tuberculosis the conjunctival reaction gave a negative result, but the subcutaneous a positive one. Two patients gave positive conjunctival and negative subcutaneous reactions, one of the patients certainly having tuberculosis (bacilli) and the other being a suspected case.

Of 21 cases examined of apparently primary pleuritis, 9, or 43 per cent., have reacted positively, and 12, or 57 per cent., negatively. Rheumatic patients free from tuberculosis are said to often show reaction. Among 14 cases investigated I have seen one positive reaction.

I have been unable to form any sure opinion of the prognostical value of the reactions during the comparatively short period during which the observations have been carried on.

The contents of this paper may be briefly summarized as follows:

The conjunctival reaction can suitably be carried out in the following way: one drop of ½ per cent. solution of ordinary Alttuberculin is instilled into one eye of the patient, and if a negative result is obtained, the experiment is repeated with a solution of the same strength in the other eye after a lapse of at least four days.

The reaction is sometimes accompanied by fever.

A positive reaction after the first or the second trial gives good support for the diagnosis, tuberculosis; a negative reaction after both attempts tells against that diagnosis, but neither reaction is of a certainty decisive. But the conjunctival experiment, however, is probably of pretty great value as an aid to forming a diagnosis when used to supplement other methods of investigation.

BIBLIOGRAPHY.

1. Münch. med. Wochenschr., No. 51, 1907.
2. Presse med., No. 99, 1907.
3. Med. Klin., No. 6, 1908.
4. Med. Klin., No. 5, 1908.
5. Revue medic. de la Suisse romande, No. 10, 1907. Cit. in Münch. med. Wochenschr., No. 2, 1908.
6. Berl. klin. Wochenschr., No. 47, 1907.
7. Beiträge z. Klinik d. Tuberkulose, vol. ix, Part I.

L'INTRADERMO-REACTION À LA TUBERCULINE.

PAR CH. MANTOUX,
Cannes, France.

Sous le nom d'intradermo-reaction à la tuberculine, nous désignons les réactions provoquées par l'injection dans l'épaisseur du derme d'une quantité dosée de tuberculine.

La cuti-réaction de von Pirquet, et les différentes variantes qui en ont été jusqu'ici proposées; réaction par friction de la peau à la tuberculine pure, de Lignières, ou par onction avec un onguent à la tuberculine de Moro, ont un caractère commun: celui de faire pénétrer la tuberculine dans le tégument cutané en quantité absolument indéterminée. Il en est de même de réactions qui s'adressent à la sensibilité des muqueuses, l'ophtalmo-réaction de Calmette, et la rhino-réaction, récemment proposée.

A n'envisager que la cuti-réaction proprement dite on conçoit que la longueur de la scarification, que sa profondeur, que l'importance de l'hémorrhagie qu'elle provoque puisse faire varier dans des proportions considérables la quantité de tuberculine qui se résorbe au niveau de la petite plaie.

Notre procédé offre l'avantage très grand d'opérer avec une quantité dosée de toxine, et d'être certain de son absorption.

Sa technique est d'une extrême simplicité. L'instrumentation se réduit à une seringue de Pravaz stérilisable à tige graduée et munie d'un curseur, c'est à dire du modèle courant, et à une aiguille fine. Nous employons une solution à 1 pour 5000 obtenue en diluant une ampoule de 1 cent. cube de solution mère de tuberculine de l'Institut Pasteur dans 49 cent. cube d'eau physiologique. Nous en injectons une goutte soit $\frac{1}{100}$ de milligramme à la face antérieure de la cuisse. Après avoir plissé la peau, on enfonce l'aiguille presque parallèlement à sa surface; on a soin que le côté biseauté de la pointe soit tourné vers le haut et regarde par conséquent vers l'épiderme non vers l'hypoderme quand l'aiguille est en place. Chez les sujets à téguments très fin il faut enfoncer franchement l'aiguille, puis, sa pointe étant dans l'hypoderme, la reveler légèrement et aborder le derme par sa face profonde; on risque autrement de le traverser de part en part.

A ce petit tour de main près, l'opération est absolument analogue à une injection traçante de cocaine; l'aiguille bien fixée, on pousse le liquide qui forme une petite boule d'oedème rapidement résorbée.

La réaction quand elle est positive est d'une extrême netteté. Elle apparait au bout de quelques heures sous forme d'une infiltration seulement perceptible au palper, ou déjà visible et de couleur blanche ou rosée. Au bout de 24 heures l'infiltration, très accrue, est rose ou rouge vif, parfois blanche oedemateuse avec une surface légèrement granitée, très rarement piquetée de deux ou trois points purpuriques. Tout autour apparait un halo rosé d'érythème. Au bout de 48 heures, la réaction atteint son acmé; nodule central et halo périphérique se sont encore développés; parfois une zone intermédiaire les sépare et accentue encore l'aspect en cocarde de la réaction.

Les dimensions de la région infiltrée, rarement inférieur à une pièce de 50 centimes, dépassent souvent celles d'une pièce de 2 francs. Avec le halo périphérique la réaction peut atteindre la surface d'une paume de main. A son niveau la peau est chaude, un peu sensible à la pression.

La réaction régresse dès le deuxième jour: le halo disparait vite; le nodule infiltré prend une teinte violacée ou bistre et se résorbe lentement. Toujours perceptible pendant quelques jours, il est souvent encore visible au bout de plusieurs semaines. Parfois l'épiderme desquame à son niveau.

Les phénomènes généraux sont habituellement nuls: deux de nos malades ont dependant présenté une réaction thermique l'un à 39°, l'autre à 38.3°; le surlendemain de l'injection.

Quand la réaction est négative on observe parfois au niveau de la piqûre une légère vaso-dilatation, un petit point d'induration. Surtout perceptibles quelques heures après l'injection, ces phénomènes s'atténuent rapidement et ont presque toujours disparu au bout de deux jours, avors que la véritable réaction est à son acmé: il n'est donc guère possible de les confondre avec celle-ci.

Nous avons pratiqué l'intradermo-réaction chez 75 sujets âgés de 3 mois à 15 ans, dans le service de notre Maitre le professeur Hutinel, à la Clinique des Enfants Malades; elle a été comparé chez 67 à la cuti-réaction.

Tous les enfants au nombre de 38 qui avaient réagi à la cuti ont réagi à l'intradermo; chez 8 dont la cuti avait été négative ou douteuse l'intradermo s'est montrée positive.

Chez 4 de ces 8 malades on a pu démontrer l'existence de la tuberculose. En effet un de ces sujets était un tuberculeux pulmonaire; un autre un tuberculeux péritonéal; 2 autres atteints l'un de néphrite l'autre d'épilepsie ont fait des réactions thermique de 38.3° et de 39° à l'injection sous cutanée de Tuberculine. Il n'a pas été possible, pour des motifs indépendants de notre volonté, de pratiquer chez les 4 autres cette épreuve. Par contre l'intradermo à fait défaut, comme la cuti, chez 2 tuberculeux pulmonaires cachectiques et chez un ménigitique moribond.

On voit que l'intradermo-réaction tout en présentant la même simplicité

d'éxécution et la même innocuité que l'épreuve de Von Pirquet, et s'en s'appliquant comme celle-ci aux malades fébriles, donne des résultats incomparablement plus nets et plus durables.

Elle est, en outre bien plus sensible: 8 enfants, c'est à dire a peu près le quart de ceux qui n'avaient réagi à la cuti ont réagi à l'intradermo. Von Pirquet, d'ailleurs sur 58 sujets reconnus tuberculeux à l'autopsie n'avait eu pendant la vie que 31 cuti positives, contre 17 négatives.

Une expérience plus longue permettra de déterminer, si seul les tuberculeux réagissent, et si tous les tuberculeux non cachectiques et non moribonds réagissent. Mais dès maintenant nous savons que l'intradermo comme la cuti, révèlent aussi bien les tuberculoses latentes que les tuberculoses appréciables à l'examen: 11 seulement de nos sujets, sur les 46 ayant réagi à l'intradermo étaient cliniquement tuberculeux.

La fréquence des réactions positives à l'intradermo crôit avec l'âge comme croit la fréquence des tuberculoses latentes: chez 8 enfants de trois mois à un an, l'intradermo a été constamment négative; chez 14 enfants de 1 an à 3 ans elle a été 9 fois négative et 5 fois positive; chez 19 enfants de 3 ans à 7 ans 9 fois négative et 10 fois positive; chez 24 enfants de 7 à 12 ans 3 fois négative et 19 fois positive; enfin 10 sujets de 12 à 15 ans ont tous réagi positivement.

L'intradermo-réaction, pratiquée à plusieurs reprises chez un même sujet a gardé les mêmes caractères; elle a semblé cependant se produire avec une intensité un peu plus grande, comme si le sujet avait été sensibilisé pour les injections précédentes.

L'injection sous-cutanée de 2 décimilligrammes de tuberculine a fait réaparaitre, chez 2 malades, la réaction qui était presque éteinte: cette réaction seconde est entrée en régression et a disparu beaucoup plus vite que la réaction primitive.

Enfin une intradermo, pratiquée quelques jours après une injection sous-cutanée de 2 décimilligrammes de tuberculine, s'est montrée égale en intensité à l'intradermo qui avait été faite avant l'injection sous-cutanée; mais elle a évolué beaucoup plus vite; elle était à son acmé au bout de 24 heures, et déjà très régressée au bout de 48 heures.

Quel parti le clinicien pourra-t-il tirer de l'intradermo et comment devra-t-il l'interpreter?

Si dans un cas donné elle est négative son absence fournira un argument de très haute valeur pour rejeter l'hypothèse d'une tuberculose.

Si elle est, au contraire, positive, on n'en devra rien conclure, sinon que l'individu est porteur d'un foyer tuberculeux. Et l'on devra se garder d'en déduire, par une erreur de raisonnement trop souvent commise, que les symptomes cliniques dont on cherche l'origine sont de nature tuberculeuse. Si un bronchitique suspect réagit à l'intradermo on devra simplement porter

le diagnostic de bronchite, chez un sujet porteur d'un foyer de tuberculose, et non celui de bronchite tuberculeuse.

On pourra seulement tenir ce diagnostic pour probable s'il s'agit d'un sujet très jeune, en raison de la rareté, dans le premier âge, des tuberculoses latentes.

L'intradermo ne permettra donc jamais, pas plus qu'aucune des épreuves à la tuberculine (exception faite pour la réaction au foyer tuberculeux que donne parfois la sous-cuti), de faire la démonstration de la nature tuberculeuse d'une lésion. Mais mieux qu'aucune autre des épreuves cutanées et muqueuses, plus commodément que l'épreuve sous-cutanée, elle permettra de rejeter quand elle sera négative le diagnostic de tuberculose.

L'intradermo pourra encore se montrer d'une grande utilité en donnant aux médecins des indices immédiatement visibles, mesurables même, sur la sensibilité des sujets à la tuberculine. On sait que la grande difficulté du traitement de la tuberculose par la tuberculine consiste à déterminer, après chaque injection, si le sujet est encore sensibilisé ou déjà immunisé à la toxine, s'il est en phase négative ou positive. En administrant la tuberculine par voie intradermique, il semble que l'on pourra tirer de l'intensité de la réaction des indications précieuses. Elles seront en tous cas d'une constatation très aisée, et plus à la portée des praticiens que celles fournies par la méthode si délicate des opsonines.

Qu'il nous soit permis, en terminant de renvoyer à une autre communication, faite à ce même Congrès; les résultats acquis chez l'homme nous ont amenés à appliquer, en collaboration avec le professeur Moussu, ce procédé diagnostique aux animaux, et nous avons pu constater qu'il se confirmait entièrement chez les bovidés les moutons, les chèvres et les porcs.

Conclusions.

Nous désignons sous le nom d'intradermo réaction à la tuberculine les réactions provoquées par l'injection, dans l'épaisseur du derme, d'une quantité dosée de tuberculine.

Sa technique, très simple, est celle de toute injection intradermique; cependant chez les sujets à peau très fine il convient d'enfoncer franchement l'aiguille jusque dans l'hypoderme, puis de relever légèrement sa pointe, et d'aborder le derme par sa face profonde; on évite ainsi de la transpercer de part en part.

Nous injectons, à la face antérieure de la cuisse une goutte de sérum artificiel contenant un centième de milligramme de tuberculine.

Les réactions extrêmement nettes sont à leur acmé au bout de 48 heures et restent constatables pendant plusieurs jours.

L'apparition de l'intradermo n'est pas empêchée par l'injection sous

cutanée de tuberculine, faite préalablement; elle réapparait d'une façon passagère quand on pratique l'injection sous-cutanée de tuberculine.

L'intradermo, qui peut cependant faire défaut chez les cachectiques et les moribonds est bien plus sensible que la cuti.

Aussi l'intradermo négative signifie-t-elle: absence de tuberculose avec un degré de certitude beaucoup plus grand que la cuti négative. Par contre l'intradermo positive signifie simplement: présence d'un foyer tuberculeux; il s'agit très souvent d'un foyer de tuberculose latente sans rapport avec les symptômes constatables cliniquement.

La fréquence des intradermo positives croit avec l'âge comme celles des tuberculoses latentes.

La voie intradermique en renseignament directement sur la sensibilité du sujet, pourra être utilisée dans le traitement de la tuberculose par la tuberculine.

L'expérimentation sur l'animal, faite en collaboration avec le professeur Moussu, a entièrement confirmé les résultats que nous avions obtenus chez l'homme.

QUELQUES ESSAIS RÉPÉTÉS DE CUTI-TUBERCULINATION.

PAR L. GUINARD,

Médecin Directeur des Sanatoriums de Bligny.

A la séance du 11 Juillet, 1907, de la Société d'études scientifiques sur la tuberculose, j'ai présenté les résultats que j'avais obtenus dans une première série d'essais de cuti-tuberculination, comprenant 72 malades. Conformément à ce que j'annonçais, j'ai poursuivi ces essais et ce sont les faits que j'ai relevés, sur une nouvelle série de 130 malades, que je me propose d'exposer dans cette courte communication.

Avant cela, il me paraît utile de rappeler certains points ressortant de mes premières observations, et d'abord, qu'il ne paraît pas y avoir accoutumance à la cuti-tuberculination et que, même à des intervalles assez rapprochés, on peut obtenir des réactions en série aussi positives et aussi caractéristiques.

En second lieu, le phénomène s'est montré si inconstant, si irrégulier dans son apparition, dans son intensité et dans ses caractères, même chez des malades incontestablement tuberculeux, que sa signification diagnostique m'a paru devoir être réservée.

Pour mes nouveaux essais, j'ai continué da faire usage d'une tuberculine précipitée, parfaitement sèche, préparée par l'Institut Pasteur. Cette tuberculine, mise en solution aqueuse à la dose de un gramme pour cinquante grammes d'eau, était conservée en tubes scèllés èt à l'abri de la lumière.

J'ai toujours opéré par scarifications d'environ quinze millimètres de long; scarifications faites au vaccinostyle et, chaque fois, j'avais grand soin de rendre le contact aussi parfait que possible on frottant l'érosion, imprégnée de tuberculine, avec le dos de l'instrument. On avait toujours soin, aussi, de laisser sècher à l'air libre le sillon tuberculiné, pendant environ dix minutes.

Ayant toujours opéré dans les mêmes conditions, je crois mes résultats aussi comparables que possible et il n'y a pas la moinde apparence que les irrégularités constatées puissent être mises sur le compte de la technique opératoire.

Je ne décrirai pas les caractères de la réaction, la chose ayant déjà été faite nombre de fois dans les divers travaux et analyses publiés sur ce sujet. S'il y a lieu, je signalerai simplement les quelques particularités que j'ai observées en plus de l'induration, de l'épaississement, de l'oedème, du halo, etc., dont l'intensité variable constitue les différents types de réaction franche ou forte et de réaction ébauchée ou faible.

Sur 130 sujets, dont 129 átteints de tuberculose pulmonaire, soumis à la cuti-tuberculination et en ne notant d'abord que le résultat de la toute première épreuve, faite sur chacun d'eux, j'ai obtenu: 64 réactions franches; 30 réactions faibles ou ébauchées; 36 résultats absolument nuls.

Les 64 sujets ayant réagi positivement, comprennent: 19 tuberculoses au 1 degré; 13 tuberculoses au 2 degrés; 31 tuberculoses au 3 degrés; plus un enfant de quatorze ans ayant toutes les apparences d'une parfaite santé.

Les 30 cuti-réactions faibles et ébauchées ont été observées sur: 5 malades au 1 degré; 1 malade au 2 degré; 24 malades au 3 degré.

Enfin, les cuti-réactions négatives groupaient: 3 malades au 1 degré; 1 malade au 2 degré; 32 malades au 3 degré.

En ajoutant à ces 130 essais, les 72 premiers dont j'ai antérieurement rendu compte, j'arrive au total de 202 épreuves, dont l'ensemble des résultats peut être résumé dans le tableau ci dessous:

Degré de T. P.	Nombre de Malades.	Réaction Franche.	Réaction Faible.	Réaction Négative.
1 degré.....	57	43 = 75, 43%	9 = 15, 78%	5 = 8, 77%
2 degré.....	23	20 = 86, 95%	2 = 8, 69%	1 = 4, 34%
3 degré.....	118	37 = 31, 35%	34 = 28, 81%	47 = 39, 83%
Sujet sain.....	4	4	34 = 28, 81%	47 = 39, 83%
Total.....	202	104	45	53

L'examen de ces rèsultats confirme le fait déjà signalé de l'irrégularité et de l'incertitude de la cuti-réaction. Sans que l'on puisse en donner la raison, sauf pour 14 malades très gravement atteints et aux dernières limites de leur résistance, nous comptons 53 tuberculeux avérés, soit 26% de ceux soumis à l'épreuve, dont 5 au premier degré et en très bon état de défense, qui n'ont pas réagi.

Remarquant par contre, que des sujets adolescents ou adultes que rien ne permet de croire entachés de bacillose, réagissent franchement à la cuti-tuberculination, il me semble que la valeur diagnostique de cette méthode mérite encore très sérieusement d'être réservée. Cependant, par la comparaison des chiffres qui figurent sur le tableau précédent, il est intéressant de remarquer que peu nombreux sont les malades, au deuxième et au premier

degré, qui ne réagissent pas, tandis que, toutes proportions gardées, il y a un plus grand nombre de 3 degré, insensibles à l'action locale cutanée de la tuberculine. C'est également dans les troisièmes degré que les différences entre chaque mode de réaction sont les moins tranchées.

Il est connu que les tuberculeux cachectiques, très gravement atteints et aux dernières limites de leur résistance sont généralement insensibles à la cuti-réaction. Pourtant, j'ai noté pas mal d'exceptions et, dans mes observations, je trouve des phtisiques, presque à la veille de mourir, qui nous ont donné des réactions très franches et très caractérisées. Par exemple, un malade atteint d'une tuberculose caséeuse extensive en pleine activité, dont il est mort peu de temps après son entrée au Sanatorium, a été éprouvé six fois et, chaque fois, a réagi très positivement; la dernière épreuve ayant précédé de très peu le jour du décès. Je vois encore un autre malade atteint depuis longtemps d'une tuberculose fibro-caséeuse bi-latérale avec cavernes, arrivé dans la dernière phase de la phtisie, faisant couramment de la température et ne pouvant pas quitter le lit, qui a réagi très vivement à une première cuti-tuberculination; les essais ultérieurs ont été négatifs. Je pourrais citer encore trois autres tuberculeux dans des conditions identiques qui ont présenté des réactions positives.

Ma deuxième série de 129 malades, parmi lesquels 85 ont été soumis systématiquement à des cuti-tuberculinations répètées et prolongées a été assez féconde en particularités que je crois instructives. Dans ces essais, les applications cutanées de tuberculine, par scarification, étaient faites tous les huit jours dans les condition rapportées plus haut.

Les épreuves ont été répètées pendant:

5 and 6 semaines pour 29 malades.
8 and 10 semaines pour 20 malades.
11 and 15 semaines pour 22 malades.
16 and 20 semaines pour 7 malades.
21 semaines pour 3 malades.
23 semaines pour 2 malades.
24 semaines pour 1 malade.
25 semaines pour 1 malade.

Je ne tiens compte dans mes appréciations que des résultats que j'ai pu observer très régulièrement et dont, chaque fois, j'ai pu vérifier les caractères.

Un premier point doit être retenu, c'est que, généralement, chaque tuberculeux soumis à des cuti-réactions répètées semble affecten un type de réaction particulier, lequel, sauf quelques variantes, domine pendant toute la durée des essais. C'est ce que j'ai constaté sur 70 de mes 85 malades éprouvés, et parmi ces 70, 39 ont eu des réactions surtout positives et franches, 31 des réactions à dominante faible ou nulle.

En retenant l'attention sur les deux extrêmes, je trouve 18 malades,

comprenant 5 premiers degré, 4 deuxièmes degré et 9 troisièmes, ayant toujours, sans exception, réagi positivement pendant 6, 10, 15, 16, 21 and 22 semaines; et 14 malades, comprenant 3 premiers degré et 11 troisièmes degré, n'ayant pas présenté la moindre ébauche de réaction, même aprés 7, 8, 12, 15, 23 et 25 épreuves.

Quinze malades ont présenté des résultats panachés, comprenant un mélange, en proportions variables, irrégulièrement ou alternativement associés, de réactions franches, faibles ou nulles, et cela sans qu'il soit possible, pour le moment, de trouver une explication, pas plus dans les conditions des essais que dans la forme, la marche et le degré de la maladie.

D'après ces constatations, il me semble que l'on peut répondre de suite aux deux questions que nous nous étions posées au début de ces recherches, à savoir: à la suite d'une série de cuti-tuberculinations peut on observer une sensibilisation croissante de l'organisme ou, au contraire, une immunisation relative à l'action locale de la tuberculine?

Le fait bien observé que sur 85 malades, 39 ont eu des réactions répètées, presque toujours franches, 31 des réactions faibles ou nulles et 15 des réactions panachées, n'est en faveur ni de la sensibilisation, ni de l'immunisation.

Toutefois, je trouve dans ma série 3 malades dont les réactions successives pourraient faire croire à des phénomènes de sensibilisation:

1. Un sujet au troisième degré, très gravement atteint, d'ailleurs décédé en cours d'épreuve, qui après deux épreuves, l'une négative, la seconde ébauchée, en a présenté une troisième très franchement positive.

2. Deux malades au 1 degré qui présentèrent une cuti-réaction franche, l'un après quatre, l'autre après cinq essais négatifs.

Inversement, huit malades pourraient être considérés comme ayant présenté des phénomènes d'accoutumance et d'immunisation relative.

D'abord quatre malades au premier degré qui, après avoir réagi très positivement, ont cessé d'être sensibles au contact de la tuberculine, un premier après la quatrième épreuve; deux autres après la cinquième, le quatriéme après la quinzième seulement; celui-ci ayant eu, après cela, une suite de quatre épreuves faiblement ébauchées.

En second lieu, deux malades, au deuxième degré, dont un sorti du Sanatorium depuis un an, en très bon état, revenu simplement pour se reposer un mois. Ce malade dont les foyers pulmonaires semblent d'ailleurs éteints, n'a pas rechuté depuis qu'il a repris son travail. Soumis à l'épreuve cutanée de la tuberculine, il a montré une réaction positive suivie d'une réaction faible, puis d'un résultat nul. Le deuxième était aussi en très bon état du côté pulmonaire, étant à fin de cure. Après quatre réactions très violentes, suivies de deux autres également positives, mais plus modérées, ce malade n'a eu que des réactions ébauchées au nombre de 9, parmi lesquelles se sont intercalées cependant deux réactions positives.

Enfin, deux tuberculeux au troisième degré ont montré, l'un une réaction très faible après six positives, l'autre six réactions négatives après une série de six réactions franches.

Est-on autorisé à considérer ces faits comme des phénomènes de sensibilisation ou d'immunisation relative? Je n'ose vraiment pas répondre par l'affirmative. Comme pour la valeur diagnostique et la signification pronostique il y a de telles irrégularités dans l'ensemble des observations que je viens d'exposer, qu'il me parait impossible de tirer des déductions ayant quelque valeur précise. Du reste; il n'y a pas plus de précision dans les résultats des essais de M. Jules Lemaire* touchant l'influence des injections sous cutanées de tuberculine sur la cuti-réaction et je ne pense pas, comme le suppose l'auteur dans son si intéressant travail, que l'on puisse espérer des résultats assez constants pour, à l'heure actuelle, entrevoir des applications réellement pratiques de la cuti-réaction.

Au nombre des particularités que j'ai encore notées et qui peuvent être retenues, je signalerai les suivantes:

1. Des phénomènes de reviviscence, nettement produits chez 4 sujets réagissant habituellement très fort aux applications locales cutanées de la tuberculine.

Ces quatre sujets comprenaient: un malade au troisième degré, deux malades au premier degré et un enfant de quatorze ans, selon toutes apparences en parfaite santé et indemne de tuberculose, lequel, sur douze épreuves, en eut dix franches et très positives et deux faibles ou ébauchées.

Chez ces sujets, en répétant les cuti-tuberculinations à des intervalles de 8 jours, j'ai vu les cicatrices de réactions positives antérieures rougir de nouveau et devenir le siège d'un mouvement réactionnel très accusé, sous l'influence d'une scarification ultérieure également positive.

Je crois que ces faits sont à rapprocher de la reviviscence des réactions locales étudiée d'abord par Koch, puis par Turban, Rumpf & Guinard, qui s'observent quelquefois chez les sujets que l'on soumet à des injections sous-cutanées thérapeutiques répétées de tuberculine. De même nature aussi doivent être les phénomènes de reviviscence de cuti et d'ophtalmo-réaction, provoqués par des injections hypodermiques de tuberculine et signalés par Jules Lemaire, S. Lévi, Calmette et Renom.

J'ai dit plus haut que les réactions positives ont présenté, avec quelques variantes suivant les individus, les différentes manifestations; rougeur, épaississement, induration, etc., qui les caractérisent; j'ai observé également la forme qualifiée d'urticarienne avec, parfois, formation de petites papules; très fréquemment aussi, dans les réactions vives, j'ai noté le halo périphérique avec couleur rouge plus ou moins fondée, parfois violacée et lie de vin, que

* "Recherches sur la cuti-réaction à la tuberculine," Rev. de la Tuberculose, Juin, 1908.

M. Jules Lemaire considère comme propre aux cuti-réactions d'une certaine intensité.

Mais, chez trois malades, notamment chez deux de ceux qui nous ont montré des phénomènes de reviviscence, les réactions avaient une très grande violence, produisaient une très large plaque épaissie et indurée avec un halo périphérique étendu; en même temps on voyait apparaitre, partant des bords de la scarification, des squames jaunâtres qui se superposaient, formant des croutelles, qui donnaient à l'ensemble un aspect très comparable aux plaques lupiques. En présence de la violence de ces réactions et des reviviscences qui les accompagnaient souvent, j'ai du, chez ces malades, espacer davantage les séances de cuti-tuberculination.

Comme particularité me paraissant encore devoir retenir quelque peu l'attention, j'ajouterai que, sans aucune modification dans la technique opératoire, on peut voir des malades au milieu d'une série continue de réactions de même forme présenter, une seule fois, un type investe des plus caractérisés. Par exemple, un malade au tout premier degré montre trois réactions franches, intercalées entre quatorze autres toutes négatives ou très faiblement ébauchées.

Un troisième degré, cavitaire, intercale une réaction nulle entre 8, et 5 très positives.

Un troisième degré, en pleine évolution de tuberculose fibro-caséeuse extensive, avec accidents congestifs et mouvements fébriles, intercale une réaction franche assez intense entre quatre réactions à peine ébauchées.

Un sujet tuberculeux au premier degré à lésions très limitées au sommet droit, ayant quelques tendances sub-fébriles, présente une réaction positive unique qui se place entre quatre réactions faibles et 7 réactions négatives.

Ces différences se rapportent-elles aux variations dans l'état de défense de l'organisme au moment de l'épreuve ou à tout autre cause modifiant sa sensibilité?. Il est très difficile de la dire; mais ces irrégularités même justifient ce que plus haut j'exprimais relativement aux incertitudes de la cuti-réaction.

Dans les essais multiples que j'ai fait, je n'ai jamais noté de phénomènes généraux, ni mouvement fébrile, ni accident secondaire, pouvant être attribué aux applications cutanées de la tuberculine. Deux fois seulement, comme M. Burnet, j'ai observé un léger oedème avec trainée lymphangitique; mais même dans les réactions les plus violentes, je n'ai jamais vu les engorgements ganglionnaires signalés par Olmer & Terras.

Enfin, une autre question pouvait se poser relativement à l'influence que des cuti-tuberculinations répétées et prolongées pourraient avoir sur la marche d'une tuberculose pulmonaire.

Or, dans la série des malades que j'ai pu suivre, parmi lesquels un certain nombre ont été soumis à des applications cutanées de tuberculine pendant

plusieurs mois, je n'ai rien observé qui m'autorise à tirer la moindre conclusion en faveur de l'influence heureuse, possible ou présumable, de ces applications.

Je ferai seulement des réserves sur certaines apparences de modifications favorables que, deux fois, j'ai cru observer, d'abord chez un enfant très légèrement glandé, d'autre part, chez un malade porteur d'adénites tuberculeuses multiples. Il s'agit peut être de simples coïncidences; mais je les retiens cependant, car si les cuti-tuberculinations répétées peuvent avoir quelque influence modificatrice sur l'organisme on ne les observera, je crois, que dans les états qualifiés de prétuberculeux ou, préventivement, chez deux individus suspects ou sujets à caution.

Conclusions.

Les irrégularités et l'inconstance trop fréquentes de la réaction provoquée par la cuti-tuberculination, chez des malades incontestablement tuberculeux et aux divers degrés de la maladie, imposent encore toutes réserves, sur la valeur pratique de cette méthode, dans le diagnostic de la tuberculose, d'autant plus que des individus d'une santé en apparence parfaite réagissent souvent très positivement.

Dans nos différentes épreuves les tuberculeux au deuxième et au premier degré se sont montrés plus sensibles et ont réagi plus régulièrement que les malades au troisième degré.

Si les tuberculeux cachectiques aux dernières périodes de leur existence sont habituellement insensibles à la cuti-tuberculination il est encore à ce fait un certain nombre d'exceptions.

Les tuberculeux soumis à des cuti-tuberculinations répétées et renouvellées tous les huit jours, pendant plusieurs mois, semblent adopter une forme de réaction particulière à chacun d'eux, laquelle, positive, ébauchée ou nulle, et sauf quelques variantes, domine pendant toute la durée de l'essais.

Les cuti-tuberculinations répétées ne paraissent conduire ni à la sensibilisation, ni à l'immunisation relative de l'organisme aux effets locaux cutanés de la tuberculine. Les quelques faits d'accoutumance (8 cas) et de sensibilisation (3 cas) que nous avons observés ne se sont pas présentés dans des conditions qui permettent de tirer des conclusions.

Au cours des cuti-réactions répétées on peut observer des phénomènes de riviviscence et voir des cicatrices d'opérations antérieures devenir le siège d'un mouvement réactionnel nouveau sous l'influence d'une scarification ultérieure positive.

Sauf peut être dans certaines localisations glandulaires et à titre tout à fait préventif, mais ces faits restent à vérifier, les cuti-tuberculinations répétées sont sans influence, sur l'évolution, la marche et l'état des accidents tuberculeux.

L'OPHTALMO-RÉACTION ET LA CUTI-RÉACTION À LA TUBERCULINE DANS LE DIAGNOSTIC PRÉCOCE, DE LA TUBERCULOSE HUMAINE.

Par le Docteur Clemente Ferreira,
São Paulo, Brésil.

Depuis le mois d'Aout 1907, aussitôt les premières communications du professeur Calmette, nous avons commencé à essayer les nouvelles méthodes —oculo-diagnostic et cuti-diagnostic—en vue de nous renseigner sur leur valeur diagnostique. Nous nous sommes efforcés de varier le plus possible les conditions de l'expérimentation et de faire des essais comparatifs en ayant recours parallèlement à l'ophtalmo-diagnostic, à la cuti-réaction et aux injections sous-cutanées de tuberculine.

Nous avons utilisé la tuberculine préparée par l'Institut de Lille et par l'Institut Pasteur et Institut sérumthérapique de Butantan à São Paulo; je me suis adressé tantôt aux petits flacons contenant cinq milligrammes de tuberculine sèche en y ajoutant, lors de l'emploi, 10 gouttes et parfois 20 d'eau distillée ou boullie, tantôt aux solutions tout faites enfermées dans des tubes compte-gouttes ou dans des tubes capillaires scellés à la lampe. Nous avons instillé généralement une goutte de la solution en faisant l'instillation tout près de l'angle interne de l'oeil contre la caroncule. Il faut tenir les deux paupières écartées et les maintenir ainsi un moment pour que la goutte ne tombe sur le rebord palpébral et que l'absorption de la tuberculine soit assurée.

Les résultats discordants que l'on constate parfois doivent être rapportés à l'expulsion de la goutte qui a lieu chez certains malades, surtout femmes et enfants, lesquels se remuent vivement et ferment violemment les paupières, surtout si par hasard la goutte de la tuberculine tombe sur la cornée. Il est des patients qui par un mouvement instinctif de défense enlèvent la goutte avec leurs mains ou frottent les yeux tout de suite après l'application, ce qui compromet encore les résultats de l'épreuve. Les fautes de technique expliquent les cas où des réactions négatives sont suivies chez les mêmes sujets de réactions positives à peu de jours d'intervalle.

Nous avons remarqué divers degrés de réaction conjonctivale; je distingue, comme plusieurs auteurs l'ont fait, une réaction faible, moyenne et forte.

La réaction faible se caractérise par une légère injection de la muqueuse qui se cantonne dans la plûpart des cas dans le coin de l'oeil, s'accompagnant d'un gonflement à peine appréciable de la caroncule. Cette réaction est fréquemment précoce et éphemère, ne se prolonge pas au delà de 24 heures.

La réaction moyenne se dénonce par le gonflement plus marqué de la caroncule, de la congestion sensible de la conjonctive palpébrale et parfois oculaire, par du larmoiement pas abondant et quelques trainées vasculaires. Cette réaction dure plus longtemps.

La réaction intense ou forte se traduit par une injection générale de toute la muqueuse conjonctivale palpébrale et oculaire, gonflement accentué de la caroncule, depôt fibrinopurulent dans le coin de l'oeil et le cul-de-sac conjonctival inférieur, gonflement œdémateux des paupières, parfois ecchymoses conjonctivales, épiphora, photophobie, enfin une véritable conjonctivite tuberculinique, qui peut se prolonger pendant dix, douze, quinze jours et un mois, d'après ce que j'ai pu observer.

Résumé des observations sur l'ophtalmo-réaction et la cuti-réaction à la tuberculine, recuellies au Dispensaire "Clemente Ferreira."

Oculo-Diagnostic.

No. 1.—A. M., homme. Suspect de tuberculose pour quelques signes physiques et des symptômes cliniques. Analyses répétées de l'expectoration négatives. Épreuve de l'ophtalmo-réaction—réaction négative. Les injections diagnostiques de tuberculine (milligr. 0.2) n'ont également pas entrainé de réaction.

No. 2.—C. M. C., femme. Tuberculose pulmonaire confirmée. Analyse du crachat positive. Épreuve de l'oculo-réaction. Réaction positive forte, qui a commencé 3 heures après l'instillation, atteignant son maximum au bout de 12 heures et disparaissant au bout de 24 heures. Température axillaire avant l'épreuve 37°, 3 heures après 37.6.

No. 3.—P. M., femme. Suspecte de tuberculose, forme asthmatique. Analyses repétées de l'expectoration négatives. Épreuve de l'ophtalmo-réaction. Réaction positive forte prolongée, persistant pendant 72 heures.

No. 4.—A. A. M., femme. Suspecte de tuberculose (anomalies de l'inspiration et submatité aux sommets). Épreuve de l'ophtalmo-réaction. réaction positive moyenne, débutant 3 heures après et disparaissant au bout de 24 heures.

No. 5.—A. S., femme. Suspecte de tuberculose pulmonaire en vue de différents phénomènes cliniques et de signes physiques. Examens du crachat toujours négatifs. Épreuve de l'ophtalmo-réaction. Réaction positive intense, se montrant tardivement, 12 heures après l'instillation et persistant pendant 15 heures.

No. 6.—A. A., femme. Tuberculose pulmonaire avérée (examen du crachat positif), guérie cliniquement et bactériologiquement (atténuation manifeste des signes physiques, augmentation du poids, disparition des bacilles, cessation de l'expectoration). Cette malade est assistée au Dispensaire depuis 1904. Épreuve de l'ophtalmo-réaction—réaction oculaire —négative.

No. 7.—A. C., homme. Tuberculose confirmée. Analyse de l'expectoration positive. Épreuve de l'ophtalmo-réaction. Réaction positive franche, débutant 4 heures après l'instillation et atteignant son maximum 20 heures plus tard (rougeur et gonflement de la caroncule, injection vasculaire du cul-de-sac conjonctival inférieur, larmoiement).

No. 8.—M. M., femme. Suspecte de tuberculose pulmonaire pour les signes physiques et quelques symptômes cliniques. Elle ne crache pas. Épreuve de l'ophtalmo-réaction. Réaction positive forte, constatée 3 heures après et persistant pendant 48 heures. Les injections diagnostiques de tuberculine entraînent de la réaction thermique (1°).

No. 9.—S. R., homme. Suspect de tuberculose pour quelques phénomènes générales et certains signes physiques. Examen du crachat négatif. Épreuve de l'ophtalmo-réaction (2 fois). Réaction négative (2 fois). Les injections souscutanées ne provoquent aucune réaction.

No. 10.—M. M., femme. Bronchite simple. Épreuve de l'ophtalmo-réaction. Réaction négative.

No. 11.—A. M., homme. Tuberculose confirmée. Analyse de l'expectoration positive. Épreuve de l'ophtalmo-réaction. Réaction positive forte, nette au bout de 5 heures.

No. 12.—J. S., homme. Suspect de tuberculose. Il ne crache pas. Épreuve de l'ophtalmo-réaction. Réaction négative. Les injections diagnostiques de tuberculine n'entraînent aucune réaction.

No. 13.—A. F., homme. Tuberculose confirmée. Analyse de l'expectoration positive. Épreuve de l'ophtalmo-réaction. Réaction positive forte.

No. 14.—S. A., femme. Suspecte de tuberculose pulmonaire, soignée comme telle depuis quelques mois. Son père est un ancien tuberculeux, client du dispensaire depuis 1904. Épreuve de l'ophtalmo-réaction. Réaction positive forte, atteignant son maximum 10 heures après l'instillation et persistant accentuée pendant 5 jours.

No. 15.—L. G. C., femme. On ne constate rien de suspect. Épreuve de l'ophtalmo-réaction. Réaction négative.

No. 16.—B. A., femme. Suspecte de tuberculose. Pas de crachats. Épreuve de l'ophtalmo-réaction. Réaction négative.

No. 17.—P. B., femme. Suspecte de tuberculose pour quelques signes physiques (anomalies de l'inspiration). Épreuve de l'ophtalmo-réaction. Réaction positive *moyenne*, débutant cinq heures après et atteignant son maximum au bout de 18 heures.

No. 18.—N. M., femme. Suspecte de tuberculose pour les signes physiques. Elle ne crache pas. Épreuve de l'ophtalmo-réaction. Réaction positive faible, constatée 23 heures après.

No. 19.—J. A., femme. Lègers soupçons de tuberculose. Elle ne crache pas. Épreuve de l'ophtalmo-réaction. Réaction négative.

No. 20.—A. C., femme. Suspecte de tuberculose pour quelques signes physiques. Analyse de l'expectoration négative. Épreuve de l'ophtalmo-réaction. Réaction positive moyenne, constatée 24 heures après l'instillation.

No. 21.—R. F., femme. Suspecte de tuberculose pour les signes physiques. Analyse du crachat négative. Épreuve de l'ophtalmo-réaction.

Réaction positive forte, commençant 4 heures après, atteignant son maximum au bout de 18 heures et persistant pendant 2 jours.

No. 22.—A. A. M., femme. Suspecte de tuberculose (deuxième instillation, la première s'etant montrée positive moyenne). Réaction positive faible, constatée 24 heures après et persistant pendant 3 jours.

No. 23.—A. M., homme. Suspect (deuxième instillation, la première s'etant montrée négative). Réaction négative, comme à l'occasion de la première épreuve. (L'évolution de la maladie a demontré qu'il ne s'agissait point de tuberculose.)

No. 24.—A. T. P., homme. Coup de froid. Il ne crache pas. Épreuve de l'ophtalmo-réaction. Réaction négative.

No. 25.—F. M., homme. Suspect de tuberculose pulmonaire. Analyse du crachat négative. Épreuve de l'ophtalmo-réaction. Réaction positive moyenne, constatée tardivement (24 heures) et persistant 72 heures. La température axillaire, qui était de 36°6 avant l'instillation, monta au bout de 4 heures a 38° (le malade a été pris d'accidents hemoptoiques 5 jours après).

No. 26.—S. L., homme. Tuberculose reconnue par les signes cliniques. Analyse de l'expectoration 2 fois négative. Épreuve de l'ophtalmo-réaction. Réaction positive faible débutant 4 heures après l'instillation et disparaissant au bout de 48 heures.

No. 27.—M. A. S., femme. Suspecte de tuberculose pulmonaire pour quelques signes peu marqués. Épreuve de l'ophtalmo-réaction (solution de tuberculine à 1 p. 200). Réaction négative.

No. 28.—A. D. A., homme. Suspect pour quelques signes physiques accentués. Le premier examen de l'expectoration a été négatif. Épreuve de l'ophtalmo-réaction (solution à 1 p. 200). Température axillaire avant l'instillation 37°6, après 37°5. Réaction positive faible, commençant 3 heures après et persistant faible jusqu'à 23 heures plus tard. Le deuxième examen du crachat, pratiqué 2 jours après l'oculo-réaction, démontre l'existence de bacilles de Koch.

No. 29.—F. C., femme. Légèrement suspecte. Épreuve de l'ophtalmo-diagnostic. Réaction oculaire négative.

No. 30.—F. C., femme. Suspecte de tuberculose pulmonaire (inspiration faible et respiration prolongée aux sommets). Épreuve de l'ophtalmo-diagnostic (solution à 1 p. 200). Température axillaire avant l'instillation 36°6, 4 heures après 37°2. Réaction négative.

No. 31.—J. B. G. S., homme. Suspect de tuberculose pour quelques signes physiques. Analyse de l'expectoration négative. Épreuve de l'ophtalmo-réaction. Réaction positive forte, constatée au bout de 24 heures et persistant 3 jours.

No. 32.—A. M., homme. Tuberculose pulmonaire confirmée. Analyse du crachat positive. Fièvre. Épreuve de l'ophtalmo-réaction. Réaction positive faible, commençant 4 heures après et persistant au même degré jusqu'à 23 heures plus tard.

No. 33.—B. F., femme. Suspecte de tuberculose pulmonaire pour quelques signes physiques. Épreuve de l'ophtalmo-réaction. Réaction négative.

No. 34.—G. R., femme. On ne constate rien de suspect chez elle. Épreuve de l'ophtalmo-diagnostic. Réaction négative.

No. 35.—J. M., femme. Suspecte (anomalies de l'inspiration). Analyse du crachat négative. Épreuve de l'ophtalmo-réaction. Réaction positive faible, débutant 3 heures après et atteignant son maximum au bout de 23 heures.

No. 36.—G. C., femme. Suspecte en raison d'avoir cohabité avec des parents tuberculeux. Toux sèche, amaigrissement et quelques signes physiques. Première épreuve. Réaction négative. Deuxième épreuve quelques jours après. Réaction positive moyenne, constatée 24 heures après l'instillation.

No. 37.—G. M. O., femme. Suspecte (anomalies de l'inspiration). Épreuve de l'ophtalmo-diagnostic. Réaction positive forte, constatée 4 heures après et persistant pendant 24 heures.

No. 38.—A. M., femme. Suspecte pour les signes physiques constatés. Analyse de l'expectoration négative. Épreuve de l'ophtalmo-diagnostic. Réaction positive forte, constatée 23 heures aprèes.

No. 39.—C. F. M., femme. Suspecte pour les signes physiques. Elle ne crache pas. Épreuve de l'ophtalmo-réaction. Température axillaire avant l'instillation 37°, 4 heures après 37°1. Réaction positive moyenne, constatée 23 heures après.

No. 40.—M. C., femme. Suspecte pour les signes physiques. Épreuve de l'ophtalmo-réaction. Réaction négative.

No. 41.—C. A., femme. Tuberculose avérée. Analyse de l'expectoration négative. Épreuve de l'ophtalmo-diagnostic. Réaction positive forte, constatée 24 heures après.

No. 42.—C. A., femme. Suspecte (inspiration âpre au creux sousclaviculaire droit). Examen du crachat négatif. Épreuve de l'ophtalmo-réaction. Température axillaire avant l'instillation 37°, 3 heures après 37°2. Réaction positive faible, constatée 10 heures après et encore appréciable au bout de 24 heures.

No. 43.—P. C., homme. Suspect pour les signes physiques. Examen du crachat négatif. Épreuve de l'ophtalmo-diagnostic (sol. à 1 p. 100). Réaction oculaire négative.

No. 44.—M. L., homme. Suspect de tuberculose pour quelques phénomènes physiques. Il ne crache pas. Épreuve de l'ophtalmo-diagnostic. Réaction positive moyenne (24 heures après).

No. 45.—S. S., homme. Bronchite simple. Oculo-réaction. Réaction oculaire négative.

No. 46.—E. P., homme. Bronchite simple. Épreuve de l'ophtalmo-diagnostic. Réaction oculaire négative.

No. 47.—H. D. E., homme. Bronchite chronique. Examen du crachat négatif. Épreuve de l'ophtalmo-diagnostic. (2 fois.) Réaction oculaire négative.

No. 48.—R. W., femme. Tuberculose diagnostiquée cliniquement. Examen du crachat négatif. Epreuve de l'oculo-réaction. Réaction positive moyenne.

No. 49.—J. D., femme. Dyspepsie. Épreuve de l'ophtalmo-diagnostic. Réaction oculaire négative.

No. 50.—A. R. G., femme. Suspecte de tuberculose pulmonaire pour quelques signes physiques. Analyse de l'expectoration négative. Épreuve de l'ophtalmo-réaction. Réaction oculaire positive faible.

No. 51.—J. T., femme. Suspecte. Examen du crachat négatif. Épreuve de l'ophtalmo-réaction. Réaction négative.

No. 52.—R. W., femme. (Deuxième épreuve.) Tuberculose diagnostiquée cliniquement. Réaction oculaire positive moyenne.

No. 53.—V. O., homme. Tuberculose confirmée par les signes cliniques et l'examen du crachat. Épreuve de l'oculo-réaction. Réaction positive moyenne.

No. 54.—F. P., homme. Tuberculose confirmée par les signes cliniques et la présence de bacilles de Koch dans l'expectoration (deuxième degré de Turban). Épreuve de l'ophtalmo-diagnostic. Réaction positive forte. (Elle persista vive pendant 6 jours et réclama l'application d'un collyre.)

No. 55.—J. R., femme. Tuberculose pulmonaire confirmée par les signes cliniques. Examen du crachat négatif. Épreuve de l'ophtalmo-diagnostic. Réaction oculaire forte. Légère augmentation de la température axillaire—37—37°2, 24 heures après.

No. 56.—P. I., homme. Asthme symptomatique de polypes nasaux. Quelques soupçons à l'égard de tuberculose. Épreuve de l'ophtalmo-diagnostic. Réaction oculaire négative. Injections diagnostiques de tuberculine; pas de réaction.

No. 57.—P. O., homme. Suspect pour quelques signes physiques. Examen du crachat négatif. Épreuve de l'ophtalmo-réaction. Réaction positive moyenne.

No. 58.—A. C. S., femme. Suspecte (son père est tuberculeux avéré, soigné au dispensaire.) Rien d'anormal à l'examen physique. Pas de bacilles dans les crachats. Ophtalmo-diagnostic. Réaction négative.

No. 59.—A. P., homme. Suspect pour quelques signes physiques. Il ne crache pas. Épreuve de l'ophtalmo-diagnostic. Réaction oculaire forte (constatée 24 heures après l'instillation).

No. 60.—R. D., femme. Suspecte (une fille est soignée au dispensaire). Examen de l'expectoration négatif. Prémière épreuve; réaction positive faible. Deuxième épreuve (7 jours plus tard); réaction positive moyenne (maximum au bout de 24 heures).

No. 61.—M. R., femme. Bronchite simple. Épreuve de l'ophtalmo-diagnostic; réaction oculaire négative.

No. 62.—E. P. M., femme. Suspecte. (La mère est morte tuberculeuse, une soeur tuberculeuse assistée par le dispensaire.) Elle ne crache pas. Première épreuve. Réaction positive faible (constatée 24 heures après). Deuxième épreuve (4 jours après); réaction oculaire négative. Le deuxième essai négatif a été probablement dû à un défaut de technique. L'observation ultérieure a démontré la nature tuberculeuse de la maladie.

No. 63.—M. C., femme. Suspecte pour des phénomènes physiques. Pas de bacilles dans les crachats. Épreuve de l'ophtalmo-réaction; réaction positive moyenne (constatée 24 heures après).

No. 64.—A. L. S., femme. Tuberculose pulmonaire démontrée par les signes cliniques et l'examen positif de l'expectoration. Épreuve de l'ophtalmo-diagnostic; réaction positive forte. À la suite de la constatation du résultat positif de l'épreuve l'analyse du crachat a decélé la présence de bacilles.

No. 65.—M. L., homme. Tuberculose confirmée par les signes clinique

et l'épreuve bactériologique. Épreuve de l'ophtalmo-diagnostic; réaction positive forte.

No. 66.—A. M., enfant agé de 5 ans. Tuberculose pulmonaire avérée avec de bacilles dans l'expectoration; tuberculose abdominale. Etat très avancé des lésions. Épreuve de l'ophtalmo-réaction; réaction oculaire négative.

No. 67.—A. N., homme. Suspect pour quelques signes physiques. Il ne crache pas. Première épreuve; réaction négative. Deuxième épreuve (tuberculine préparée à l'Institut de Butantan); réaction douteuse (le malade est atteint d'une hyperémie conjonctivale habituelle). Injection sous-cutanée de tuberculine; aucune réaction.

No. 68.—E. P. M., femme. Deuxième instillation; réaction négative comme lors de la première.

No. 69.—F. P. M., femme. Suspecte (la mère et deux frères plus agés sont morts de tuberculose pulmonaire). Épreuve de l'ophtalmo-diagnostic; réaction positive moyenne.

No. 70.—R. D., femme. Suspecte pour des phénomènes physiques aux sommets. Examen du crachat négatif. Deuxième épreuve; réaction positive moyenne comme lors de la première instillation.

No. 71.—G. J., femme. Tuberculose confirmée cliniquement (deuxième degré). Épreuve de l'ophtalmo-réaction; réaction positive forte (constatée 24 heures plus tard et durant 3 jours).

No. 72.—F. P., homme. Asthme. Examen du crachet négatif. Epreuve de l'ophtalmo-diagnostic; réaction négative.

No. 73.—A. G., homme. Suspect pour des signes physiques et les symptômes cliniques. Prémière épreuve (14 Octobre 1907); réaction négative. Deuxième épreuve (4 jours après); réaction positive faible, constatée 24 heures après. Le jour de la deuxième épreuve l'examen du crachat réalisé 5 heures après, l'instillation décèle la présence de bacilles. Peut-être un défaut de technique explique-t-il l'échec de la première épreuve.

No. 74.—J. P. C., homme. Suspect pour les signes physiques. Examen du crachat négatif. Épreuve de l'ophtalmo-diagnostic; réaction positive moyenne.

No. 75.—L. R., fillette de dix ans. Suspecte pour quelques signes physiques. (Les parents sont morts de tuberculose.) Prémière épreuve (17 Octobre 1907); réaction négative. Deuxième épreuve (18 Octobre); réaction négative. Troisième épreuve (24 Octobre); réaction négative.

No. 76.—J. P., homme. Suspect (anomalies de l'inspiration). Il ne tousse pas. Injections diagnostiques de tuberculine (méthode de Löwenstein); aucune réaction. Épreuve de l'ophtalmo-réaction; réaction oculaire négative.

No. 77.—P. G., femme. Suspecte pour quelques phénomènes physiques. Elle ne crache pas. Première épreuve (22 Octobre 1907); tuberculine préparée à l'Institut sérumthérapique de Butantan (São Paulo). Réaction négative. Deuxième épreuve (24 Octobre); la même tuberculine. Réaction négative. Troisième épreuve; tuberculine préparée à l'Institut Pasteur de Lille; réaction positive moyenne. Injections sous-cutanées de tuberculine; aucune réaction. Cuti-réaction négative.

No. 78.—C. B., garçon de 12 ans. Suspect pour quelques signes physiques. Prémière épreuve (22 Octobre 1907). Réaction négative. Deux-

ième épreuve (25 Octobre); réaction négative. Injections sous-cutanées de tuberculine; aucune réaction.

No. 79.—L. P., femme. Cardiopathie. Trois épreuves successives; réaction toujours négative.

No. 80.—A. O., femme. Suspecte pour quelques signes physiques. Elle ni tousse ni crache pas. Première épreuve (22 Octobre); tuberculine de l'Institut Butantan-São Paulo. Réaction négative. Deuxième épreuve (29 Octobre); tuberculine de l'Institut Pasteur de Lille. Réaction positive forte. L'évolution de la maladie en a demontré la nature tuberculeuse. Le résultat négatif de la prémière épreuve a été dû au viellissement de la tuberculine préparée ici, qui ne se conserve pas longtemps.

No. 81.—R. J., femme. Tuberculose confirmée par les signes cliniques. Épreuve de l'ophtalmo-réaction (24 Octobre); tuberculine de l'Institut Butantan récemment préparée. Réaction positive forte.

No. 82.—L. B. R., femme. Aortectasie. Épreuve de l'ophtalmo-diagnostic. Réaction négative.

No. 83.—G. M., femme. Tuberculose confirmée par les signes physiques et par l'examen positif des crachats. Épreuve de l'ophtalmo-réaction (24 Octobre). Réaction positive forte. L'examen du crachat a été fait le 25 Octobre, trois heures après la constatation de la réaction positive de la conjonctive.

No. 84.—C. B., homme. Cardiopathie. Suspect de tuberculose pour les signes physiques. Première épreuve (25 Octobre); tuberculine de l'Institut Butantan—São Paulo. Réaction oculaire négative. Deuxième épreuve (28 Octobre); tuberculine européenne (Institut de Lille). Réaction positive moyenne (constatée 24 heures après l'instillation et persistant pendant 72 heures). Injections diagnostiques de tuberculine; réaction thermique (38°5) à la suite de la première injection.

No. 85.—A. M. O., femme. Suspecte pour quelques phénomènes physiques. Elle ne crache pas. Première épreuve (24 Octobre); tuberculine de l'Institut de Butantan-São Paulo. Réaction négative. Deuxième épreuve (29 Octobre); tuberculine de l'Institut Pasteur de Lille. Réaction positive forte (constatée 24 heures après).

No. 86.—M. G., femme. Suspecte de tuberculose pulmonaire (anomalies de l'inspiration). Elle ne crache pas. Épreuve (le 29 Octobre); tuberculine de l'Institut Pasteur de Lille. Réaction positive forte.

No. 87.—O. C., femme. Bronchite simple. Épreuve de l'ophtalmo-diagnostic. Réaction négative.

No. 88.—A. N., homme. Dilatation du tronc brachio-céphalique. Épreuve de l'ophtalmo-réaction (le 25 Octobre). Réaction négative.

No. 89.—P. N., homme. Bronchite simple. Épreuve de l'ophtalmo-réaction (le 25 Octobre); réaction négative.

No. 90.—E. G., homme. Il ne se plaint de rien; il se montre bien portant. Épreuve de l'ophtalmo-réaction; tuberculine de l'Institut Pasteur de Lille. Réaction négative.

No. 91.—A. J. C., homme. Tuberculose confirmée cliniquement et bactériologiquement. Épreuve de l'oculo-diagnostic; tuberculine européenne. Réaction positive forte.

No. 92.—M. R., femme. Suspecte pour quelques signes physiques. Examen du crachat négatif. Épreuve de l'ophtalmo-réaction (le 29 Octo-

bre); tuberculine de l'Institut Pasteur de Lille. Réaction négative à l'examen réalisé 24 heures après l'instillation. Injections sous-cutanées de tuberculine en vue du diagnostic. Sous l'action de la deuxième injection (deux decimilligrammes) légère réaction thermique—36°4—37°5; en même temps la réaction oculaire, qui était absente depuis le jour de l'instillation, se montre sur l'oeil instillé le 29 Octobre et devient fort sensible, se prolongeant 6 jours avec une intensité marquée (sensibilisation de l'oeil sous l'influence des injections de tuberculine).

No. 93.—M. G., femme. Suspecte pour les phénomènes physiques. Elle ne crache pas. Épreuve de l'ophtalmo-diagnostic (le 29 Octobre). Réaction positive, forte constatée 24 heures après.

No. 94.—A. F., fillette de 14 ans Ankylostomasie. Épreuve de l'oculo-diagnostic. Réaction négative.

No. 95.—L. G., femme. Suspecte pour quelques phénomènes physiques. Elle ne crache pas. Épreuve de l'ophtalmo-réaction. Réaction positive forte.

No. 96.—P. S., fillette agée de 12 ans. Suspecte pour quelques phénomènes physiques. Elle ne crache pas. Épreuve de l'oculo-diagnostic. Réaction positive forte.

No. 97.—I. L., femme. Bronchite simple. Épreuve de l'ophtalmo-réaction. Réaction négative.

No. 98.—A. C., homme. Tuberculose confirmée par les signes cliniques et l'analyse de l'expectoration. Épreuve de l'ophtalmo-réaction (le 5 Novembre); Temp. axillaire avant l'instillation 38°1, 4 heures après 38°5. Réaction oculaire positive forte.

No. 99.—A. A., homme. Suspect pour quelques signes physiques. Examen du crachat négatif. Première épreuve (le 5 Novembre); tuberculine de l'Institut Pasteur à São Paulo. Réaction négative. Deuxième épreuve (le 7 Novembre); tuberculine de l'Institut Pasteur de Lille. Réaction négative. Cuti-réaction (le 12 Novembre); réaction cutanée négative.

No. 100.—F. J., homme. Suspect pour quelques signes physiques. Examen du crachat négatif. Épreuve de l'ophtalmo-réaction (le 5 Novembre). Réaction positive moyenne.

No. 101.—L. V., homme. Suspect. (Un frère tuberculeux, 2 neveux tuberculeux). Première épreuve (le 5 Novembre); tuberculine de l'Institut Pasteur de São Paulo. Réaction négative. Deuxième épreuve (le 7 Novembre); tuberculine de l'Institut Pasteur de Lille. Réaction négative.

No. 102.—R. M. J., femme. Suspecte pour les signes physiques. Examen du crachat négatif. Épreuve de l'ophtalmo-réaction. Réaction positive forte.

No. 103.—M. C., femme. Légèrement suspecte (anomalies de l'inspiration). Examen du crachat négatif. Épreuve de l'ophtalmo-diagnostic (le 7 Novembre). Réaction positive forte, persistant 6 jours et réclamant l'application d'un collyre.

No. 104.—F. P., homme. Syphilis. Épreuve de l'ophtalmo-réaction. Réaction négative.

No. 105.—D. F. X., homme. Suspect (anomalies de l'inspiration). Il ne crache pas. Épreuve de l'oculo-réaction. Réaction positive forte. Température axillaire avant l'instillation 36°9, 4 heures après 37°2.

No. 106.—F. D. C., homme. Suspect pour quelques phénomènes

physiques. Examen du crachat négatif. Épreuve de l'ophtalmo-réaction (le 13 Novembre); tuberculine européenne. Réaction positive forte.

No. 107.—M. L., homme. Entérite chronique. Épreuve de l'ophtalmo-réaction. Réaction négative.

No. 108.—F. R., homme. Syphilis. Épreuve de l'ophtalmo-réaction; tuberculine de l'Institut Pasteur de Lille. Réaction négative.

No. 109.—F. D. C., homme. Suspect de tuberculose pulmonaire pour des phénomènes physiques. Épreuve de l'ophtalmo-réaction. Réaction positive moyenne.

No. 110.—A. C., homme. Suspect. Épreuve de l'ophtalmo-réaction; tuberculine de l'Institut Pasteur de Lille. Réaction positive moyenne (24 heures après).

No. 111.—D. F. X., homme. Suspect pour les signes physiques. Épreuve de l'oculo-réaction; tuberculine de l'Institut Pasteur de Lille. Réaction positive forte (24 heures après).

No. 112.—M. L., homme. Bronchite. Épreuve de l'ophtalmo-diagnostic. Réaction négative.

No. 113.—L. A., homme. Bronchite grippale. Épreuve de l'ophtalmo-réaction; tuberculine de l'Institut Pasteur de São Paulo. Réaction oculaire négative.

No. 114.—M. G., agé de 7 ans. Suspecte de tuberculose ganglionnaire. Adénopathie trachéo-bronchique. Anhémie. Première épreuve (le 18 Octobre); tuberculine de l'Institut Pasteur de São Paulo. Réaction négative. Deuxième épreuve (le 3 Novembre); tuberculine européenne. Réaction négative. Le garçonnet à l'aide de la médication iodée et de la revulsion locale, s'est beaucoup amélioré, la toux a diminué d'une façon marquée.

No. 115.—I. F., femme. Suspecte pour quelques signes physiques. Épreuve de l'oculo-réaction; tuberculine européenne. Réaction positive forte.

No. 116.—A. A., femme. Suspecte pour quelques signes physiques. Épreuve de l'ophtalmo-réaction; tuberculine européenne. Réaction positive forte.

No. 117.—B. A., femme. Tuberculose confirmée cliniquement et bactériologiquement diagnostiquée. Épreuve de l'ophtalmo-réaction; tuberculine européenne. Réaction positive forte (24 heures après).

No. 118.—F. R., femme. Bronchite simple. Épreuve de l'oculo-réaction; tuberculine européenne. Réaction négative.

No. 119.—O. M. de C., femme. Fort suspecte pour les signes physiques et les symptômes cliniques. Température axillaire 38°. Épreuve de l'ophtalmo-diagnostic (le 21 Novembre); tuberculine de l'Institut Pasteur de Lille. Réaction positive forte.

No. 120.—M. L., femme. Suspecte pour quelques signes physiques. Elle ne crache pas. Épreuve de l'oculo-diagnostic; tuberculine européenne. Temp. 37°2 lors de l'instillation, 38°4 heures après. Réaction positive forte.

No. 121.—A. P., homme. Légèrement suspect. Épreuve de l'oculo-diagnostic; tuberculine européenne. Réaction négative.

No. 122.—E. G., femme. Légèrement suspecte pour quelques signes physiques. Pas d'expectoration. Épreuve de l'ophtalmo-diagnostic; tuberculine européenne. Réaction négative.

No. 123.—J. P., homme. Tuberculose pulmonaire confirmée par l'ex-

amen positif du crachat. Épreuve de l'oculo-diagnostic; tuberculine européenne. Réaction positive moyenne. Cuti-réaction positive.

No. 124.—A. F. O., homme. Fort suspect de tuberculose pulmonaire pour les signes physiques. Épreuve de l'ophtalmo-diagnostic; tuberculine européenne. Réaction positive forte.

No. 125.—A. J. de M., homme. Suspect pour les signes physiques. Épreuve de l'ophtalmo-diagnostic; tuberculine européenne. Réaction positive forte (24 heures après).

No. 126.—G. M., homme. Suspect pour les signesp hysiques. Il ne crache pas. Épreuve de l'ophtalmo-diagnostic; tuberculine européenne. Réaction positive moyenne.

No. 127.—M. J. da S., femme. Bronchite simple. Épreuve de l'ophtalmo-diagnostic; tuberculine européenne. Réaction négative.

No. 128.—V. A., homme. Tuberculose pulmonaire avérée depuis 1904. Épreuve de l'oculo-diagnostic; tuberculine européenne. Réaction positive forte constatée 24 heures après et persistant intense pendant 3 jours.

No. 129.—F. J. A., homme. Suspect pour les signes physiques. Il ne crache pas. Épreuve de l'ophtalmo-diagnostic; tuberculine européenne. Réaction positive forte (durant 4 jours).

No. 130.—S. D., homme. Rhinite ozénique. Pas de signes physiques appréciables du côté de l'appareil pulmonaire. Épreuve de l'ophtalmo-réaction le 29 Novembre 1907; tuberculine européenne. Réaction positive forte (constatée 24 heures après et persistant intense pendant 8 jours). (On sait que Lombard et Caboche, de Paris, considèrent l'ozène comme une forme larvée de la tuberculose nasale et les recherches cliniques de Caboche semblent donner un point d'appui sérieux à cette théorie. Lombard, qui a étudié la question avec Caboche, affirme que l'injection cutanée de tuberculine a donné des résultats positifs chez certains malades porteurs d'ozène. Le résultat positif de l'ophtalmo-réaction chez le malade de cette observation plaide en faveur de la manière de voir des auteurs ci-dessus).

No. 131.—R. K., homme. Suspect pour des phénomènes physiques. Il ne crache pas. Épreuve de l'ophtalmo-diagnostic; tuberculine européenne. Réaction positive moyenne. Température axillaire 36°6 avant l'instillation et 37°5 4 heures après. La réaction se maintient vive pendant 3 jours.

No. 132.—J. de A., homme. Suspect pour les signes physiques. Il ne crache pas. Épreuve de l'ophtalmo-diagnostic; tuberculine européenne. Réaction positive forte, appréciable et vive pendant 4 jours.

No. 133.—M. J. S., femme. Bronchite simple. Deuxième épreuve (le 29 Novembre); tuberculine européenne. Réaction négative comme lors de la première instillation.

No. 134.—M. L., garçon de 7 ans. Adénopathie trachéo-bronchique. Deuxième épreuve (le 3 Décembre); tuberculine européenne. Réaction négative. Cuti-réaction le 3 Décembre; réaction négative.

No. 135.—E. R., femme. Dyspepsie. Épreuve de l'ophtalmo-diagnostic le 3 Décembre; tuberculine européenne. Réaction négative.

No. 136.—A. P., femme. Légèrement suspecte. Épreuve de l'ophtalmo-diagnostic le 10 Décembre; tuberculine de l'Institut Pasteur de São Paulo. Réaction oculaire positive faible. Cuti-réaction le même jour; réaction cutanée positive faible.

No. 137.—L. L., femme. Légèrement suspecte. Épreuve de l'ophtalmo-diagnostic; tuberculine européenne. Réaction positive moyenne.

No. 138.—A. V., femme. Fort suspecte. On n'avait pas encore fait l'examen de l'expectoration. Première épreuve (le 15 Octobre); tuberculine de l'Institut Pasteur de São Paulo. Réaction positive faible. Deuxième épreuve (le 5 Décembre); tuberculine européenne. Réaction positive moyenne. Le même jour (le 5 Décembre) l'examen du crachat décèle l'existence de bacilles.

No. 139.—F. G., femme. Suspecte de tuberculose pulmonaire. Première épreuve (le 5 Décembre); tuberculine européenne. Réaction négative. Deuxième épreuve (le 10 Décembre); tuberculine de l'Institut Pasteur de São Paulo. Réaction négative.

No. 140.—A. C., homme. Suspect pour quelques phénomènes physiques. Examen du crachat négatif. Épreuve de l'ophtalmo-diagnostic; tuberculine de l'Institut Pasteur de São Paulo. Réaction positive forte.

No. 141.—A. A., homme. Rien d'anormal. Examen du crachat négatif. Bronchite simple. Prémière épreuve le 9 Décembre; réaction négative. Deuxième épreuve le 11 Décembre; réaction négative.

No. 142.—J. R., homme. Légers soupçons. Il ne crache pas. Cuti-réaction positive. Épreuve de l'oculo-diagnostic (1 Décembre 1907); tuberculine de l'Institut Pasteur de São Paulo. Réaction positive moyenne.

No. 143.—J. P., homme. Rien de suspect. Il ne tousse pas. Épreuve de l'ophtalmo-diagnostic; réaction négative.

No. 144.—J. O., homme. Suspect pour quelques pénomènes physiques. Examen du crachat négatif. Épreuve de l'ophtalmo-diagnostic; réaction positive faible.

No. 145.—A. R., homme. Syphilis. Épreuve de l'oculo-diagnostic; tuberculine de l'Institut Pasteur de São Paulo. Réaction négative.

No. 146.—A. G., femme. Suspecte. Épreuve de l'ophtalmo-diagnostic le 10 Décembre. Réaction positive faible.

No. 147.—J. A., femme. Suspecte pour quelques phénomènes physiques. Examen du crachat négatif. Épreuve de l'ophtalmo-diagnostic; tuberculine de l'Institut Pasteur de São Paulo. Réaction positive moyenne.

No. 148.—L. C., femme. Rien d'anormal. Prémière épreuve le 10 Décembre; tuberculine de l'Institut Pasteur de São Paulo. Réaction douteuse. Deuxième épreuve deux jours après; tuberculine de l'Institut Pasteur de São Paulo. Réaction négative. L'examen du crachat fut négatif.

No. 149.—A. A. O., femme. Suspecte pour quelques phénomènes physiques; des crachats hémoptoïques. Épreuve de l'ophtalmo-diagnostic. Réaction positive moyenne.

No. 150.—B. N., femme. Elle ne tousse ni ne crache pas. Rien de suspect. Prémière épreuve le 10 Décembre; réaction négative. Deuxième épreuve le 12 Décembre; réaction négative.

No. 151.—J. M., homme. Légèrement suspect. Examen de l'expectoration négatif. Première épreuve le 9 Décembre; tuberculine de l'Institut Pasteur de São Paulo. Réaction négative d'abord, qui devient positive sous l'action de la cuti-réaction. Deuxième épreuve le 12 Décembre; tuberculine de l'Institut Pasteur de São Paulo. *Réaction oculaire positive faible.*

No. 152.—J. R., homme. Suspect pour des signes physiques. Il ne

crache pas. Épreuve de l'oculo-diagnostic le 11 Décembre; tuberculine de l'Institut Pasteur de São Paulo. Réaction positive forte.

No. 153.—J. M., homme. Suspect pour quelques signes physiques. Il ne crache pas. Épreuve de l'ophtalmo-diagnostic. Réaction positive faible.

No. 154.—L. C., femme. Grippe. Épreuve de l'oculo-diagnostic; tuberculine de l'Institut Pasteur de São Paulo. Réaction oculaire négative.

No. 155.—L. C., femme. Bronchite simple. Épreuve de l'ophtalmo-diagnostic; tuberculine de l'Institut Pasteur de São Paulo. Réaction oculaire négative.

No. 156.—G. V., femme. Suspecte pour quelques signes physiques. Examen du crachat négatif. Épreuve de l'oculo-diagnostic le 12 Décembre. Réaction négative.

No. 157.—D. D. A., femme. Tuberculose confirmée. Épreuve de l'ophtalmo-diagnostic; tuberculine de l'Institut Pasteur de São Paulo. Réaction positive moyenne.

No. 158.—A. L., homme. Suspect pour quelques phénomènes physiques. Il ne crache pas. Épreuve de l'oculo-diagnostic. Réaction positive forte.

No. 159.—A. D., homme. Suspect. Épreuve de l'oculo-diagnostic le 16 Décembre. Réaction négative.

No. 160.—A. M., femme. Suspecte. Épreuve de l'oculo-diagnostic. Réaction négative.

No. 161.—T. A., femme. Dyspepsie. Épreuve de l'oculo-diagnostic. Réaction négative.

No. 162.—C. A., homme. Fort suspect pour des signes physiques. Il ne crache pas. Épreuve de l'ophtalmo-diagnostic; tuberculine de l'Institut Pasteur de São Paulo. Réaction positive forte. Cuti-réaction forte.

No. 163.—E. J. A., homme. Légèrement suspect. Épreuve de l'oculo-diagnostic. Réaction négative.

No. 164.—R. P., femme. Légèrement suspecte. Épreuve de l'oculo-diagnostic. Réaction oculaire négative.

No. 165.—O. C. M., femme. Légèrement suspecte. Elle ne crache pas. Épreuve de l'ophtalmo-diagnostic; tuberculine de l'Institut Pasteur de São Paulo. Réaction négative.

No. 166.—E. C., femme. Suspecte. Épreuve de l'ophtalmo-diagnostic. Réaction oculaire positive moyenne, qui persiste 3 jours.

No. 167.—A. D. F., homme. Suspect pour quelques phénomènes physiques. Épreuve de l'ophtalmo-diagnostic. Réaction positive forte.

No. 168.—A. W., femme. Suspecte pour quelques phénomènes physiques. Examen du crachat négatif. Épreuve de l'oculo-diagnostic le 26 Décembre. Réaction de l'oculo-diagnostic le 26 Décembre. Réaction oculaire positive moyenne.

No. 169.—A. A., femme. Fort suspecte. Examen du crachat négatif. Épreuve de l'oculo-diagnostic. Réaction oculaire positive forte. (Confirmation par les progrès de la maladie et l'apparition de bacilles.)

No. 170.—A. S., homme. Légèrement suspect. Examen du crachat négatif. Épreuve de l'oculo-diagnostic; tuberculine de l'Institut Pasteur de São Paulo. Réaction positive moyenne.

No. 171.—J. P. A., homme. Tuberculose cliniquement et bactériologi-

quement confirmée. Épreuve de l'oculo-diagnostic. Réaction oc[illegible] positive forte.

No. 172.—A. M., homme. Tuberculose confirmée. Épreuve de l'ophtalmo-diagnostic le 27 Décembre; tuberculine de l'Institut Pasteur de São Paulo. Réaction positive moyenne. Cuti-diagnostic, réaction cutanée négative.

No. 173.—A. D. S., enfant de 7 ans. Adénopathie trachéo-bronchique (tuberculeuse). Deuxième épreuve de l'oculo-diagnostic le 27 Décembre; tuberculine de Lille. Réaction oculaire négative.

Au total, 173 cas d'ophtalmo-diagnostic où ont été faites 195 épreuves, dont 102 se sont montrées positives, 91 négatives et 2 douteuses.

Les réactions ont été positive dans:

Cas de tuberculose confirmée par l'examen clinique et l'analyse bactérioscopique de l'expectoration	19
Cas de tuberculose confirmée par l'examen clinique	6
Cas suspects de tuberculose, chez quelques-uns desquels l'analyse de l'expectoration a été négative	77
Les réactions ont été négative dans:	
Cas de tuberculose cliniquequement et bactériologiquement confirmée et guérie	1
Cas suspects	52
Cas où il y avait tout simplement de la bronchite ou il s'agissait d'autres maladies	37
Cas de tuberculose généralisée à la phase terminale	1
Les réactions ont été douteuses dans 2 cas suspects.	

Dans plusieurs cas, des réactions négatives ont été suivis de réactions positives au bout de peu de jours, le résultat négatif étant dû à une défaillance de l'activité de la tuberculine préparée ici et conservée pendant une quinzaine de jours; l'instillation d'une tuberculine plus récente ou de la tuberculine de Lille entraînait une réaction positive.

Dans quelques cas les réactions négatives ont été constatées au bout de 24 heures, les malades ne revenant les jours suivants. Plus tard l'évolution des symptômes, le développement des signes physiques, l'apparition de bacilles de Koch dans l'expectoration sont venus indiquer la nature tuberculeuse de la maladie; de façon que, suivant toutes probabilités, la réaction se montrerait tardivement positive, s'il eût été possible d'examiner ces malades 36, 48 ou 72 heures après l'instillation. Plusieurs fois la réaction négative 24, 36 heures après, s'est montrée positive le troisième jour.

Comme le fait rémarquer fort judicieusement M. Comby, il y a un grand nombre de réactions négatives qui sont des réactions positives retardées; le médecin perdant de vue les malades observés seulement 24 heures après l'épreuve.

L'évolution de la maladie a confirmé géneralement les résultats de la réaction et ne sont pas rares les cas où, au bout de peu de temps, des phénomènes cliniques expressifs et l'examen du crachat tranchent la question. Chez

deux malades (observ. 93 et 152) la réaction d'abord inexistante se montre sensiblement nette par un phénomène de sensibilisation provoquée au premier cas sous l'influence des injections sous-cutanées de tuberculine et se développant chex le second patient sous l'action de la cuti-réaction.

VOICI LES PRINCIPALES PARTICULARITÉS REMARQUÉES PENDANT LES ESSAIS, QUE NOUS AVONS FAITS SUR L'OPHTALMO-DIAGNOSTIC.

1. Réviviscence de la réaction positive sous l'influence des injections sous-cutanées de tuberculine (soit que celles-ci entraînent ou non de la réaction thermique).

2. Réapparition d'une réaction oculaire positive dejà dissipée sous l'action de la cuti-réaction ou des injections sous-cutanées de tuberculine (2 dixièmes de milligramme).

3. Phénomènes de sensibilisation ou apparition d'une oculo-réaction positive inexistante, plusieurs jours après l'instillation (9 jours chez le malade No. 94), sous l'influence des injections positives de tuberculine. Chez la malade de l'observation 94 la réaction oculaire négative s'est montrée positive 9 jours après l'instillation conjonctivale sous l'influence de la deuxième injection de 0 millgr. 002 de tuberculine, laquelle a été suivie de réaction thermique.

4. Si l'on fait à la fois l'oculo-réaction, la cuti-réaction et les injections de tuberculine, ainsi que nous l'avons pratiqué chez plusieurs malades, les réactions peuvent se montrer toutes positives ou négatives, les unes n'exerçant pas d'action inhibitrice vis-à-vis les autres.

5. Dans certains cas l'oculo-réaction et la cuti-réaction entraînent une certaine élévation de la température générale.

6. Dans nombre de cas des malades qui n'ont pas réagi à une première épreuve d'ophtalmo-diagnostic ont présenté, sous l'action d'une deuxième ou d'une troisième épreuve, une réaction positive.

Les réactions négatives sont souvent dues à une légère faute de technique, à l'expulsion de la goutte instillée par les larmes, à un réflexe vif des paupières ou aux mouvements des mains de quelques malades. Quelquefois nous avons remarqué que l'insuccès tenait à la défaillance d'activité de la tuberculine, la réaction se montrant dès que nous avions récours à la tuberculine européenne, plus active, ou à la tuberculine plus récemment préparée par les Instituts de cette ville.

7. Il est de réactions précoces, qui se manifestent 3–4 heures après l'instillation, mais se dissipent promptement, sont éphemères, ne persistent pas, il en est d'autres fort en retard—36, 48 et 72 heures—elles peuvent tout à coup prendre une intensité rémarquable.

8. La durée de l'ophtalmo-réaction est des plus variables; en règle gén-

érale, si ce n'est les réactions abortives, qui disparaissent au bout de quelques heures—3 à 12—la plupart se prolongent pendant 24, 36 et 48 heures; il est nombre de cas où les phénomènes conjonctivaux persistent pendant 3, 4, 5, 8, et 15 jours.

Il est de différences dans l'activité de la tuberculine préparée ici et de celle qui nous vient d'Europe; plusieurs cas et une observation prolongée ont mis ce fait en lumière. La tuberculine préparée dans cette ville perd tôt son activité; au bout de 8, 10 jours cette activité va en diminuant, d'où il ressort que les résultats de l'ophtalmo-diagnostic se montrent discordants jusqu'à ce que les réactions deviennent toutes négatives, voire dans les cas cliniquement et bactériologiquement confirmés. La tuberculine préparée en Europe garde son activité pendant longtemps—1, 2 et 3 mois—sans présenter des défaillances appréciables.

Ce sont là des particularités qu'il faut mener en ligne de compte pour trouver l'explication de certains faits disparates.

Conclusion.—Les nombreux cas, recueillis au Dispensaire depuis Aout 1907 jusqu'à ce jour (environ 500), confirment l'assertion du professeur Calmette "que l'ophtalmo-diagnostic de la tuberculose a fait ses preuves de fidelité et d'innocuité. On a eu chez nous recours à cette épreuve chez des tuberculeux cliniquement et bactériologiquement avérés, chez ceux dont le *report microscopique* et la séméiologie clinique ont établi la maladie, chez des patients tout simplement suspects et chez ceux atteints de plusieurs autres maladies.

D'une façon générale les résultats ont confirmé les conclusions déduites par le savant directeur de l'Institut Pasteur de Lille, et par les drs. Comby, Ausset, Grasset, Letulle, Desplats, Guinon, Bazy en France, Citron et Fritz Lévy en Allemagne, Derscheid en Belgique, Exchaquet, Bourget et Hensler en Suisse, Baldwin aux E'tats Unis; ont été fort rares les faits où la réaction conjonctivale a manqué de se montrer chez des malades manifestement atteints de tuberculose.

Essais de Cuti-réaction à la Tuberculine.

No. 1.—P. G., femme. Suspecte de tuberculose pulmonaire. Épreuve de l'oculo-diagnostic et injections de tuberculine négatives. Cuti-réaction le 12 Novembre. Pas de réaction cutanée.

No. 2.—F. R., homme. Rien d'anormal. Cuti-réaction le 12 Novembre. Pas de réaction cutanée. Épreuve de l'ophtalmo-diagnostic le 13 Novembre; pas de réaction oculaire et pas de sensibilisation de la réaction cutanée.

No. 4.—J. P., homme. Tuberculose confirmée. Cuti-diagnostic le 25 Novembre. Réaction cutanée positive moyenne. Température axillaire avant, 37°8, après l'essai, 38°2.

No. 5.—A. de F. O., homme. Fort suspect pour les signes physiques. L'épreuve de l'ophtalmo-réaction a été positive et forte. Cuti-diagnostic le

25 Novembre. Réaction cutanée faible, mais reviviscence de la réaction conjonctivale.

No. 6.—A. J., de M., homme. Suspect pour des phénomènes physiques. Il ne crache pas. L'épreuve de l'oculo-diagnostic, pratiquée le 22 Novembre, a été positive et forte. Cuti-diagnostic le 25 Novembre. Réaction cutanée forte, constatée le 26; elle s'évanouit le 29, l'oculo-réaction se maintenant encore.

No. 7.—O. M. C., femme. Tuberculose confirmée par l'examen positif de l'expectoration. Épreuve de l'oculo-réaction le 21 Novembre; réaction positive forte. Cuti-diagnostic le 26 Novembre; Réaction cutanée positive forte, visible jusqu'au 28 Novembre.

No. 8.—S. D., homme. Suspect. Oculo-réaction positive forte, atténuée mais encore appréciable au moment où l'on pratique la cuti-réaction. Réaction cutanée positive au bout de 24 heures et disparaissant au bout de 72 heures. L'oculo-réaction s'exacerbe sous l'influence de la cuti-réaction.

No. 9.—R. K., homme. Suspect de tuberculose pulmonaire pour les signes physiques. Oculo-réaction positive. Cuti-diagnostic le 2 Décembre; réaction cutanée positive forte pendant 48 heures.

No. 10.—P. G., homme. Signes physiques suspects. Oculo-réaction positive. Cuti-diagnostic le 5 Décembre; réaction cutanée négative. La suite de la maladie a confirmé les soupçons, démontrant la fidelité de l'oculo-réaction.

No. 11.—T. J., femme. Légèrement suspecte. Elle ne crache pas. Première épreuve de l'oculo-réaction négative. Deuxième épreuve de l'ophtalmo-réaction le 10 Décembre; au même jour cuti-diagnostic. Réaction oculaire négative. Cuti-réaction positive faible.

No. 12.—A. P., femme. Légèrement suspecte. Elle ne crache pas. Prémière épreuve de l'oculo-réaction le 3 Décembre; tuberculine européenne. Réaction oculaire positive faible. Deuxième épreuve de l'ophtalmo-diagnostic le 10 Décembre; tubercuiine de l'Institut Pasteur de São Paulo. Cuti-diagnostic le même jour. Réaction oculaire et réaction cutanée positives faibles.

No. 13.—J. P., homme. Rien de suspect. Réaction oculaire négative. Cuti-diagnostic 3 jours après; réaction cutanée négative.

No. 14.—A. A., homme. Bronchite aigue. Pas de bacilles dans l'expectoration. Cuti-diagnostic le 4 Décembre 1907; réaction négative. Épreuve de l'ophtalmo-diagnostic le 9 Décembre; réaction oculaire négative.

No. 15.—J. M., homme. Légèrement suspect. Examen du crachat négatif. Cuti-diagnostic le 11 Décembre; réaction cutanée négative. Oculo-réaction négative.

No. 16.—J. R., homme. Suspect pour les signes physiques. Examen du crachat négatif. Cuti-diagnostic le 4 Décembre; réaction cutanée positive moyenne, que persiste pendant 3 jours.

No. 17.—S. A., femme. Dyspepsie. Cuti-diagnostic le 19 Décembre et oculo-diagnostic le même jour. Réactions oculaire et cutanée négatives.

No. 18.—A. M., femme. Anhémie. Cuti-diagnostic et ophtalmo-diagnostic le 19 Décembre 1907; réactions négatives.

No. 19.—C. A., homme. Tuberculose pulmonaire confirmée. Cuti-diagnostic et ophtalmo-diagnostic le 19 Décembre; réactions oculaire et cutanée positives fortes.

No. 20.—R. B., femme. Tuberculose pulmonaire, troisième degré Turban; diagnostic clinique et bactériologique. Cuti-diagnostic et ophtalmo-diagnostic le 19 Décembre 1907; réactions oculaire et cutanée positives et faibles.

No. 21.—M. de S., femme. Chloro-anhémie. Cuti-diagnostic et ophtalmo-diagnostic le 19 Décembre; réactions négatives.

No. 22.—E. de C., femme. Suspecte de tuberculose pulmonaire pour quelques signes physiques. Elle ne crache pas. Cuti-diagnostic et ophtalmo-diagnostic le 19 Décembre; réactions cutanée et oculaire positives moyennes.

No. 23.—O. M., femme. Suspecte pour quelques signes physiques. Elle ne crache point. Cuti-diagnostic et ophtalmo-diagnostic le 19 Décembre. Oculo-réaction négative; cuti-réaction positive le 20 Décembre. Le 22 Décembre sous l'influence de la cuti-réaction la réaction oculaire se montre positive et nette (sensibilisation).

No. 24.—E. J. A., homme. Suspect (bronchite chronique, père tuberculeux avéré, une sœur est morte enlevée par la tuberculose). Examen du crachat négatif. Cuti-diagnostic et ophtalmo-diagnostic le 29 Décembre; réactions oculaire et cutanée négatives.

No. 25.—A. L., homme. Suspect pour quelques phénomènes physiques. Analyse du crachat négative. Oculo-diagnostic le 16 Décembre; réaction oculaire positive faible (24 heures après). Cuti-diagnostic le 20 Décembre; réaction cutanée positive moyenne (le 25 Décembre) et reviviscence de l'oculo-réaction.

No. 26.—A. D. F., homme. Suspect pour quelques signes physiques. Il ne crache pas. Première épreuve de l'oculo-diagnostic négative. Première épreuve de cuti-diagnostic le 20 Décembre; réaction cutanée positive faible constatée le 21. Deuxième épreuve de l'ophtalmo-diagnostic et deuxième épreuve de cuti-diagnostic le 26 Décembre; réactions oculaire et cutanée positives faibles.

No. 27.—R. A. de P., femme. Suspecte pour quelques signes physiques. Elle ne crache pas. Cuti-diagnostic le 26 Décembre; réaction cutanée positive moyenne.

No. 28.—R. V. de S. P., femme. Tuberculose pulmonaire confirmée par l'examen positif des crachats. Cuti-diagnostic le 26 Décembre; réaction cutanée positive forte.

No. 29.—M. A., femme. Légers soupçons. Examen du crachat négatif. Cuti-diagnostic le 26 Décembre; réaction cutanée positive faible.

No. 30.—C. M. D., homme. Signes physiques probants. Examen du crachat positif. Cuti-diagnostic et oculo-diagnostic le 27 Décembre 1907. Oculo-réaction positive moyenne; réaction cutanée négative.

Les malades, chez lesquels la réaction cutanée s'est montrée positive, continuent en assistance et les symptômes se sont accentués de façon qu'il ne reste aucune doute sur la nature de la maladie.

Total 30 cas, où nous avons eu recours à 31 cuti-réactions.
Les résultats ont été positifs dans:
19 cas et négatifs dans 11.

La réaction cutanée a été positive dans:	
Cas de tuberculose confirmée par les signes physiques et l'examen positif de l'expectoration	4
Cas de tuberculose confirmée par les signes cliniques	1
Cas suspects de tuberculose par les signes physiques, chez quelques-uns desquels l'analyse du crachat a été négative	14
La réaction cutanée a été négative dans:	
Cas suspects pour quelques signes physiques	4
Cas de tuberculose avérée avec l'examen du crachat positif	1
Cas de maladies non tuberculeuses	6

Les réactions ont été négatives chez les malades No. 10 et No. 30, dont l'un était fortement suspect et avait présenté déjà une réaction oculaire positive, la suite de l'affection en démontrant la nature tuberculeuse; et l'autre (No. 30) présentait des bacilles dans les crachats et avait réagi positivement à l'ophtalmo-diagnostic.

Notre pratique démontre donc que la cuti-réaction est moins fidèle que l'ophtalmo-diagnostic. Cette épreuve mérite cependant d'être mise plus largement à essai, vu qu'il s'agit d'un procédé inoffensif et bien accepté par les malades.

Les réactions de la peau, de même que les réactions conjonctivals, ne sont pas en rapport avec l'étendue des lésions.

Nous avons commencé depuis quelques mois le traitement de la maladie à l'aide de l'insertion cutanée de la tuberculine; pour le moment les résultats sont encourageants, la réaction étant nulle ou à peine de 2 à 3 dixièmes de degré.

Conclusion.—Le cuti-diagnostic ou réaction de von Pirquet constitue une épreuve d'une valeur diagnostique non négligeable. Il s'agit là d'un procédé simple, bien accepté des patients et exempt de tout inconvénient. La réaction cutanée entraîne quelquefois une exacerbation de la réaction conjonctivale ou même une reviviscence, lorsqu'elle est employée 2 à 3 jours à la suite de l'oculo-diagnostic. La cuti-réaction commence le plus fréquemment 24 heures après l'épreuve; elle persiste ordinairement 2 à 4 jours.

La cuti-réaction est moins fidèle que l'ophtalmo-réaction, d'après ce qui ressort des faits observés par nous.

L'inoculation cutanée de tuberculine provoque parfois une légère élévation de la température axillaire.

L'inoculation cutanée de tuberculine, au moyen de scarifications pareilles à celles que nous pratiquons lors de la vaccination anti-variolique, semble procurer des résultats favorables dans le traitement de la tuberculose pulmonnaire; ce procédé n'entraîne pas de réaction marquées et constitue une bonne voie d'introduction de cet agent. Nous recommandons l'emploi plus large de ce procédé de tuberculino-thérapie, destiné, ce nous semble, à rendre aux malades des services précieux.

The Ophthalmic and Cutaneous Reaction to Tuberculin in the Early Diagnosis of Human Tuberculosis.—(FERREIRA.)

Conclusions on Ophthalmic Reaction.—The numerous cases observed at the dispensary since August, 1907, to this day (about 500), confirm the assertion of Calmette, "that the ophthalmo-diagnosis of tuberculosis has proved to be certain and harmless." We have used this test in tuberculous patients clinically and bacteriologically determined as such, in patients simply suspected, and in those affected with several other maladies.

In general it can be said that the results have confirmed the conclusions of Calmette and other observers, and that the conjunctival reaction was [illegible] very rarely in patients manifestly afflicted with tuberculosis.

Conclusions on Cutaneous Reaction.—The cutidiagnosis or reacti[illegible] von Pirquet constitutes a test of a not negligible diagnostic value. In it we have a simple procedure, easily accepted by the patient, and free from all inconvenience. The cutaneous reaction sometimes brings about an exacerbation of the conjunctival reaction, or even its reappearance, when it is employed two or three days after the ophthalmic test. The cutireaction begins more frequently twenty-four hours after the test, and persists ordinarily two to four days.

The cutaneous reaction is not so certain as the ophthalmo-reaction, according to facts observed by us.

The cutaneous inoculation of tuberculin sometimes provokes Ferreira, ophthalmic, and cutaneous reaction.

A Slight Elevation of the Axillary Temperature.—The cutaneous inoculation of tuberculin, by means of similar scarifications to those used for ordinary vaccination, seems to produce favorable results in the treatment of pulmonary tuberculosis; this procedure is not followed by marked reactions, and constitutes a good route for the introduction of this agent. We recommend the employment on a larger scale of this method of tuberculin therapy, which, it seems to us, is destined to render valuable services to the sick.

[END OF JOINT SESSION OF SECTIONS I AND II.]