

**Tuberculin in diagnosis and treatment : a text-book of the specific diagnosis and therapy of tuberculosis for practitioners and students / By Dr. Bandelier ... and Dr. Roepke.**

**Contributors**

Bandelier, B. 1871-1924.  
Roepke, Otto, 1870-1942  
Christopherson, Wilfred B.  
Augustus Long Health Sciences Library

**Publication/Creation**

New York : W. Wood and Company, 1913.

**Persistent URL**

<https://wellcomecollection.org/works/ajekaurb>

**License and attribution**

This material has been provided by This material has been provided by the Augustus C. Long Health Sciences Library at Columbia University and Columbia University Libraries/Information Services, through the Medical Heritage Library. The original may be consulted at the the Augustus C. Long Health Sciences Library at Columbia University and Columbia University. where the originals may be consulted.

This work has been identified as being free of known restrictions under copyright law, including all related and neighbouring rights and is being made available under the Creative Commons, Public Domain Mark.

You can copy, modify, distribute and perform the work, even for commercial purposes, without asking permission.



Wellcome Collection  
183 Euston Road  
London NW1 2BE UK  
T +44 (0)20 7611 8722  
E [library@wellcomecollection.org](mailto:library@wellcomecollection.org)  
<https://wellcomecollection.org>



COLUMBIA LIBRARIES OFFSITE  
HEALTH SCIENCES STANDARD



HX64123863

RC311 .B223

Tuberculin in diagno

**RECAP**

**TUBERCULIN IN  
DIAGNOSIS AND TREATMENT**

BY

**BANDELIER & ROEPKE**

RC311  
B223



RC311

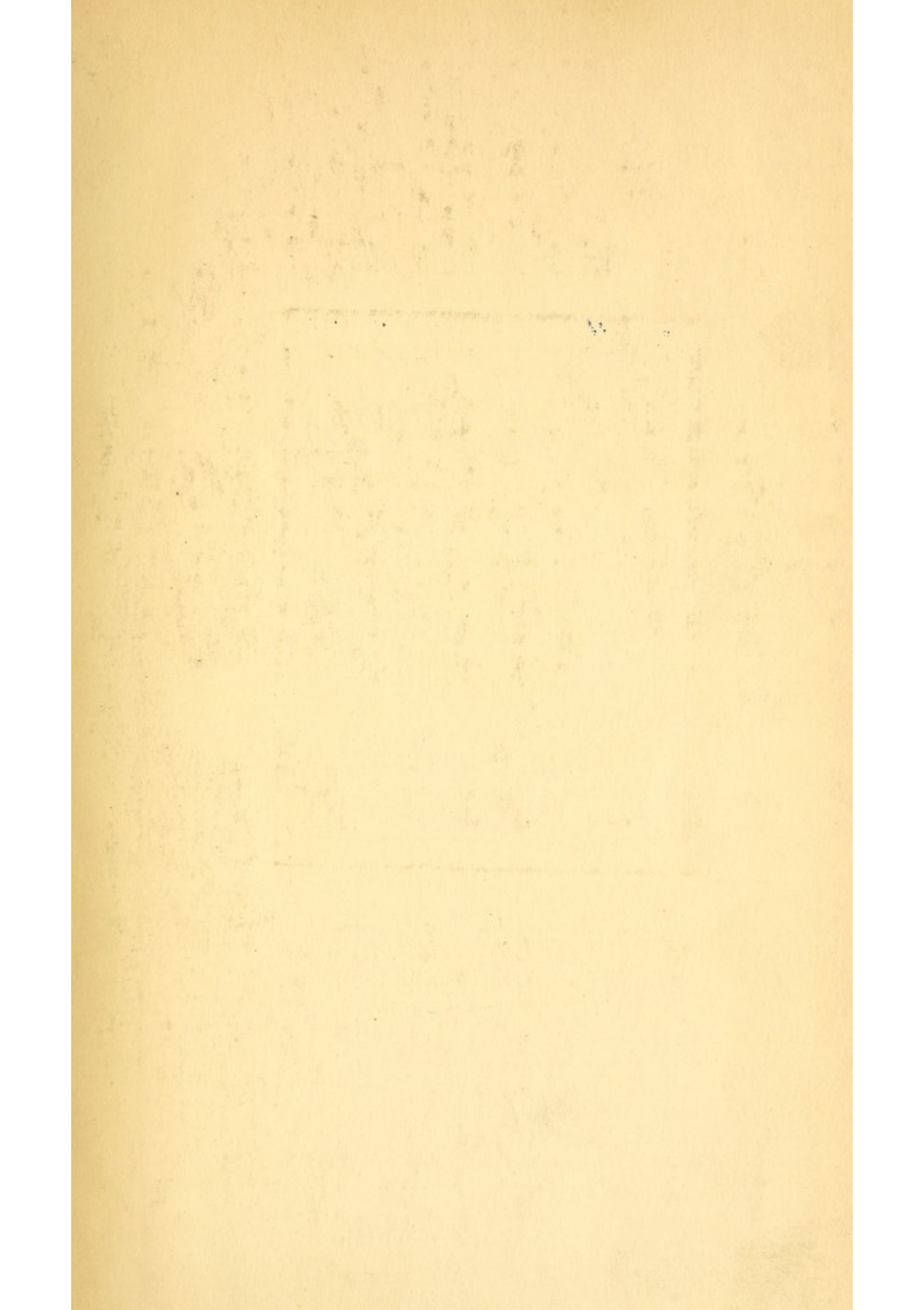
B223.

**Columbia University  
in the City of New York**

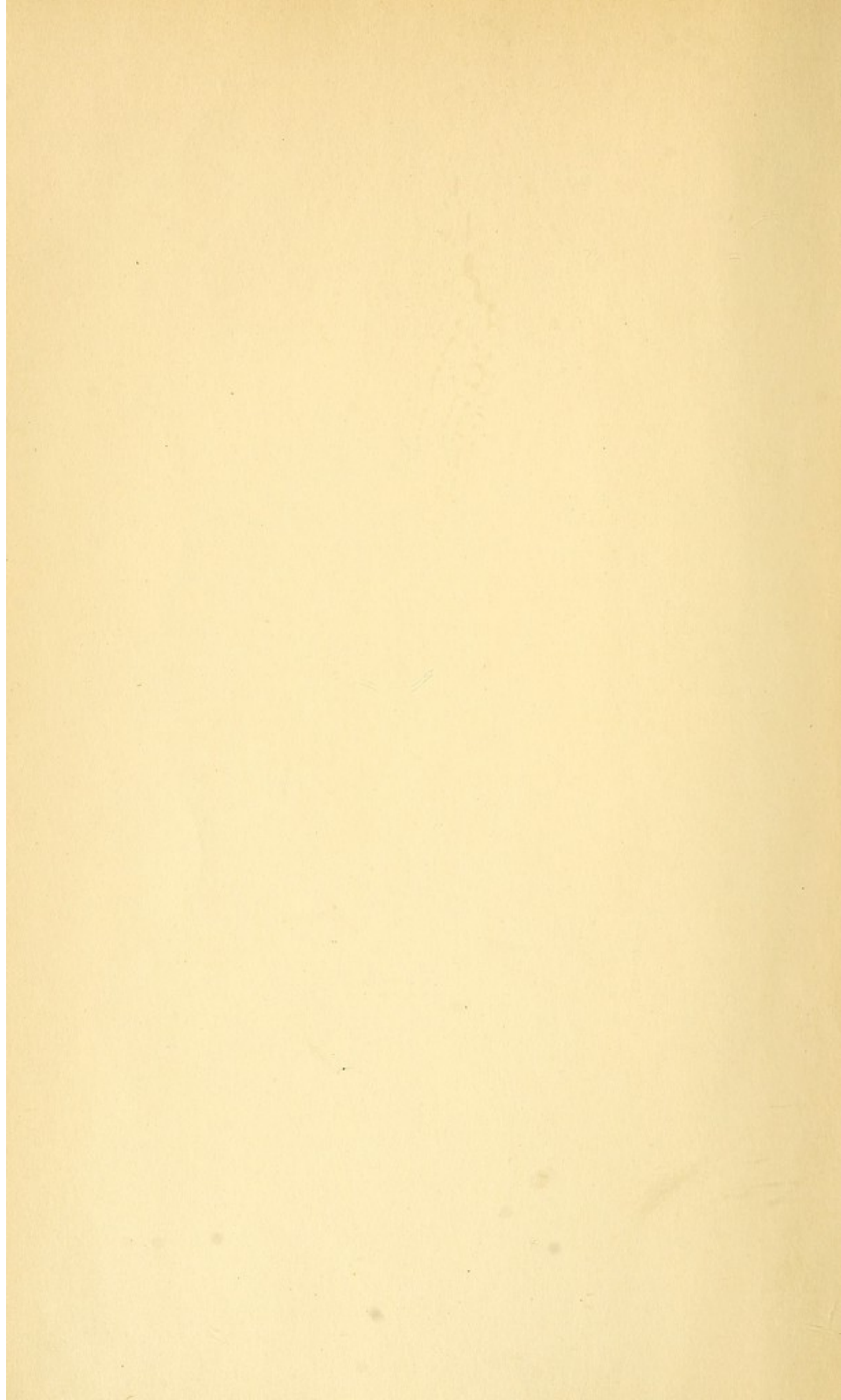
**College of Physicians and Surgeons  
Library**














TUBERCULIN IN  
DIAGNOSIS AND TREATMENT





Digitized by the Internet Archive  
in 2011 with funding from  
Open Knowledge Commons

To the great Master

Robert Koch



GERMAN TUBERCULOSIS CLASSICS

*Issued on the advice and under the direction of*

EGBERT MORLAND, M.D., B.Sc.

COLLEGE  
UNIVERSITY  
LIBRARY

# TUBERCULIN IN DIAGNOSIS AND TREATMENT

A Text-book of the Specific Diagnosis and Therapy  
of Tuberculosis

For Practitioners and Students

BY

Dr. BANDELIER

AND

Dr. ROEPKE

*Medical Director of Sanatorium  
"Schwarzwaldheim" at Schömberg  
(Wildbad)*

*Medical Director of the Railway  
Sanatorium "Stadtwald" at  
Melsungen (Cassel)*

SECOND ENGLISH EDITION

TRANSLATED FROM THE SEVENTH REVISED AND ENLARGED  
GERMAN EDITION

BY

WILFRED B. CHRISTOPHERSON

*With Twenty-five Temperature Charts, Two Coloured Lithographic Plates,  
and Five Illustrations in the Text*

NEW YORK

WILLIAM WOOD AND COMPANY

MDCCCCXIII.





## Translator's Note.

THE present second English edition of "Tuberculin in Diagnosis and Treatment" is a translation from the seventh German edition of the "Lehrbuch der Spezifischen Diagnostik und Therapie der Tuberkulose." Apart from the addition of side-headings, the omission of a few notes unimportant to English readers and the conversion of doses from cubic centimetres to cubic millimetres in accordance with other recent English text-books, the work has been translated literally. The book has been rendered into English on the basis of Dr. E. C. Morland's translation from the second German edition (1909), which now forms but a small part of the whole.

I acknowledge with many thanks the valuable assistance of Dr. E. C. Morland in the translation and of Dr. G. B. Hunt in the revision of the proof-sheets. I have drawn on a translation of the sixth German edition supplied by Dr. D. M. Barcroft. The publishers of the German edition—Messrs. Curt Kabitzsch, of Würzburg—were good enough to send me their advance sheets; by this means the translation has appeared very shortly after the publication of the original.

W. B. CHRISTOPHERSON,  
Laboratory of Clinical Research,  
Arosa, Switzerland.

*July, 1913.*





## Authors' Preface.

"TUBERCULIN in Diagnosis and Treatment," four years after its first appearance, has reached its seventh edition, has been translated into seven foreign languages, and the English and Russian versions are now in their second edition. This success is the result of the unanimous and hearty appreciation which has been accorded to the several editions in all the medical literature at home and abroad. The appearance of the book met a very real need and the form in which it was presented filled a gap. We have attempted to fulfil the last wish of R. Koch with regard to the subject of tuberculosis and tuberculin, written on May 12, 1909: "To maintain the same high standard in the later editions of their book which are certain to follow." This hope of the master could not be dishonoured; it made the work entailed by each succeeding edition a thankoffering to the great physician who has taught us to recognize tuberculosis as a popular plague and to treat it successfully.

The value of this bequest has also been an incentive to the enlargement and complete revision of the present seventh edition. Further, various critics have advised certain abridgments, enlargements and alterations. One objected to the increasing size of the book and feared that it might suffer in case of reference and teaching value and thereby in interest for details of practical importance; he advised more rigid treatment of matter and of the views of other authorities. Another critic required, in addition to all details of theory and practice, a more extensive treatment of certain sections, more diagrams to illustrate the text, &c.—in short, enlargement rather than abridgment. Then came the practitioners demanding by mouth and pen a more exact explanation of the specific processes, of the nature of the tuberculin reaction and the healing action of tuberculin.

In order to accede to all justifiable requests, the new edition, which had in the meantime become necessary, could hardly be reduced in size; on the contrary, an enlargement was unavoidable. In order to restrict this to definite limits and not to hamper the clear description of specific diagnosis and treatment, all matter relating to theory, which was previously scattered in the various



chapters, has now been collected into a special section, completed and condensed. It follows the introduction, which describes the present condition of tuberculosis and the tuberculin question. The theoretical section leads on to the practical conduct of the specific diagnosis and treatment of tuberculosis. In describing the theory of the subject we have had to be short and concise, but, in spite of the difficulties entailed by the numerous views still in circulation, we hope to have laid a foundation on which clinicians and practitioners may understand and conduct modern tuberculin treatment.

The specific diagnosis of tuberculosis has remained separated in the general and special sections. The former has been enlarged to include a more detailed description and a coloured illustration of the intracutaneous test, the latter a chapter on the specific diagnosis of tuberculosis of the digestive organs and some new charts to show tuberculin reactions. In both sections the literature of the last few years bearing on the value and province of tuberculin diagnosis has been critically and extensively noticed.

We have made more important changes in describing the specific treatment of tuberculosis. In the first place parts of the general and special sections have been respectively interchanged in order to treat one of the most important chapters—that dealing with the specific treatment of pulmonary tuberculosis—more clearly and convincingly. In addition the text has, on the one hand, been freed from many unimportant and unsettled details and, on the other, has been completed by the inclusion of all important advances in the province of specific therapy. We hope that the present enlargement is free from omissions and—apart from our own experiences, which increase from year to year—describes the views of both advocates and opponents in an equally unbiased manner. We have only left undescribed what must appear to all competent judges as purely superficial and irrational methods of treatment, not as rational tuberculin therapy.

In the general section dealing with specific treatment, chief attention has been paid as before to the most trustworthy of the actively immunizing preparations. All other known preparations and results of therapeutic research, according to their present significance, have been more or less completely or summarily described as the case may be. We should have considered ourselves ill-advised to discuss only those specific remedies in very general use, tested and found of value, and to reject all others. We hope, by the clear division of matter and arrangement of text, to have considerably allayed the fear that the increasing



size of the book would make reference a matter of greater difficulty. The international character of the work compelled us to make it no mere general outline but a genuine text-book which should supply to every reader an explanation with regard to any required subject. The physician should be able to afford information on any specific remedy brought to his notice by advertisement; and of these various remedies there is now no small number.

In the special section of specific treatment a chapter is added dealing with tuberculosis of the digestive organs; all other chapters have been carefully enlarged in accordance with present-day knowledge, the several organs receiving separate treatment.

In the enlarged concluding section we have treated the matter from the standpoint of consistent but unbiased positivism and excluded the personal note. It is intended to convert to our views the opponents of specific measures, a section of the medical fraternity becoming smaller and smaller but not yet completely convinced, and at the same time to encourage the diagnostic and therapeutic use of tuberculin both in the institution and in general practice. We feel justified in defining and fixing its sphere owing to more than ten years' work in the specific diagnosis and treatment of tuberculosis and a wealth of varied personal experience inside and outside the sanatorium which can hardly have been afforded to any other physician. And we feel it our bounden duty to aid the victorious progress of tuberculin through all hospitals, health resorts for tuberculosis and sanatoria, and where its valuable action will be displayed in a still higher degree—through the ranks of the practitioners.

So much for the explanation of the motives, the nature and the compass of the present revised and enlarged seventh edition. The general aim of the whole has remained the same. May this volume in its new form receive a kindly reception and add to the friends of earlier editions fresh champions for the fight against the national disease, tuberculosis—with the aid of specific diagnosis and treatment.

THE AUTHORS.

*Melsungen and Schömberg,*

*December, 1912.*

# ERRATUM.

Page 9, line 18 from top, *for* "clinicians, Grace" *read*  
"clinicians, Crace."



## Robert Koch's Introductory Note to the Third Edition.

It gives me great pleasure to accede to the request of one of the authors of "Tuberculin in Diagnosis and Treatment" that I should write a short introduction to the 3rd edition of this work.

In my first publications on the subject of tuberculin, I pointed out both the diagnostic and therapeutic value of this remedy. But for a long time tuberculin failed to receive the consideration due to it in either of these directions. The reason was obviously that our knowledge of how to attain artificial immunity was insufficient, and therefore a right understanding of the specific effect of the remedy and the extent to which it could be used was lacking. Consequently results were expected from tuberculin when it was no longer a question of pure tuberculosis at all, but of mixed infections with exciting causes of suppuration and of influenza, then widespread. For the same reason the fable of the "tubercle bacillus rendered mobile" was believed in, and, indeed, if I am not mistaken, it still haunts many a brain.

Only since the doctrine of immunity has been more and more studied and understood by physicians have right conceptions been formed as to the method of applying tuberculin and the nature of its effect, and once more physicians are beginning to turn its valuable properties to good effect. This change of opinion as regards tuberculin has been largely due to the fact that, by the use of the Opsonic Index and the technique for the Fixation of Complement, methods were found which made it possible to check the effect of the remedy, whereas before a purely empirical judgment had to be formed. Moreover, the splendid successes gained by veterinary surgeons in the diagnosis of bovine tuberculosis and more recently the v. Pirquet method, which has so extraordinarily simplified the diagnostic use of tuberculin in the treatment of human beings, have once more drawn attention to tuberculin.

From all quarters, especially from abroad, reports are now coming in of scientific research work dealing with the specific treatment of tuberculosis. In the first place it was the specialists in tuberculosis who made use of tuberculin treatment; but now that it has been shown that tuberculin can also be used with advantage



and without any danger by the skilled physician in private practice, it would appear that many practitioners are desirous of following this example. But there is an obstacle in the way, for it is difficult for the physician who does not happen to have an opportunity of getting the requisite information from a specialist to obtain the necessary particulars as to the selection of the preparation and the right application of the same. For during the course of the last few years more than a dozen specific preparations made from the culture fluid of the tubercle bacilli or from the substance of the bacilli themselves have been recommended for the treatment of tuberculosis, and it is obvious that they cannot all be equally valuable. Moreover, opinion is still very much divided as to the best method of treatment. And as reports on the various preparations and on the methods of treatment are widely scattered in the literature of the subject, some considerable study is needed to form an opinion on the present condition of the specific treatment of tuberculosis.

Under these circumstances, it was a very praiseworthy task to collect and consider critically all that is known of the specific diagnosis and treatment of tuberculosis for the needs of the practitioner. This task has been undertaken by Dr. Bandelier and Dr. Roepke and most skilfully carried out, as is clearly proved by the rapid succession of the editions of their text-book. But, apart from this, I have satisfied myself that this latest edition is not a mere compilation of extracts from the literature, but a reliable guide for all those who wish to put the specific treatment into practice.

I should also like to draw special attention to the fact that I agree with the authors that when specific remedies are used rise in temperature must be avoided as far as possible, but that it is not advisable continuously to give only the smallest doses, as recommended in many quarters. It must not be forgotten that here it is a question of active immunization, and that it can only be to the advantage of the patient that not too low a degree of immunity should be attained.

I should like to state that I also agree in recommending specific treatment for out-patients, naturally with the most careful selection of cases.

May the authors maintain the same high standard in the later editions of their book, which are certain to follow.

R. KOCH.

*Berlin,*

*May 12, 1909.*



# Contents.

	PAGE
<b>Introduction</b> ... ..	1
<b>I.—Theoretical Part</b> ... ..	12
<b>A.—THEORIES OF TUBERCULIN REACTION</b> ... ..	13
1.—CHANGES IN THE TOXIN-SENSITIVE CELLS ... ..	13
2.—THE TOXIN THEORY ... ..	16
3.—THE AMBOCEPTOR THEORY OF WOLFF-EISNER ... ..	18
4.—THE THEORIES OF HYPERSUSCEPTIBILITY ... ..	19
5.—THE THEORY OF NON-SPECIFIC ACTION ... ..	22
<b>B.—THE CURATIVE FACTORS OF TUBERCULIN ACTION</b> ... ..	24
1.—TOX-IMMUNITY ... ..	24
2.—THE FOCAL REACTION ... ..	27
3.—THE ANTIBODIES AS CURATIVE FACTORS ... ..	28
(a) Antitoxins ... ..	28
(b) Agglutinins ... ..	29
(c) Opsonins ... ..	30
(d) Phagocytosis ... ..	33
(e) Bacteriotropins and Bacteriolysins ... ..	35
(f) Complement-fixing Antibodies ... ..	36
<b>II.—The Specific Diagnosis of Tuberculosis</b> ... ..	37
<b>A.—GENERAL SECTION</b> ... ..	37
1.—THE CUTANEOUS TUBERCULIN TESTS ... ..	38
(a) Cutaneous Test according to v. Pirquet ... ..	38
(b) Percutaneous Tuberculin Test of Moro ... ..	49
(c) Intracutaneous Tuberculin Test ... ..	54
2.—THE CONJUNCTIVAL TUBERCULIN TEST ... ..	58
3.—THE SUBCUTANEOUS TUBERCULIN TEST ... ..	69
<b>B.—SPECIAL SECTION</b> ... ..	93
1.—TUBERCULIN DIAGNOSIS IN TUBERCULOSIS OF THE LUNG ... ..	93
2.—TUBERCULIN DIAGNOSIS IN TUBERCULOSIS OF THE RESPIRATORY TRACT ... ..	106
3.—TUBERCULIN DIAGNOSIS IN TUBERCULOSIS OF THE DIGESTIVE ORGANS ... ..	109
4.—TUBERCULIN DIAGNOSIS IN UROGENITAL TUBERCULOSIS ... ..	111
5.—TUBERCULIN DIAGNOSIS IN TUBERCULOSIS OF THE SEROUS MEMBRANES ... ..	113
6.—TUBERCULIN DIAGNOSIS IN OPHTHALMIC TUBERCULOSIS ... ..	115
7.—TUBERCULIN DIAGNOSIS IN AURAL TUBERCULOSIS ... ..	117
8.—TUBERCULIN DIAGNOSIS IN TUBERCULOSIS OF THE SKIN ... ..	118
9.—TUBERCULIN DIAGNOSIS IN TUBERCULOSIS OF THE GLANDS, BONES AND JOINTS ... ..	121
10.—TUBERCULIN DIAGNOSIS IN CHILDREN'S DISEASES ... ..	123



	PAGE
<b>III.—The Specific Treatment of Tuberculosis</b> ... ..	129
<b>A.—GENERAL SECTION</b> ... ..	129
1.—GENERAL PRINCIPLES OF TUBERCULIN TREATMENT ... ..	132
2.—METHOD AND GENERAL TECHNIQUE OF MODERN TUBERCULIN TREATMENT ... ..	139
3.—THE SPECIFIC REMEDIES FOR TUBERCULOSIS ... ..	158
(a) Preparations Designed to produce Active Immunity ... ..	159
(1) Old Tuberculin (AT) ... ..	159
(2) Albumose-free Tuberculin (AF) ... ..	164
(3) New Tuberculin (TR) ... ..	167
(4) New Tuberculin Bacillary Emulsion (BE) ... ..	169
(5) Sensitized Bacillary Emulsion (SBE) ... ..	173
(6) Landmann's Tuberculol... ..	175
(7) The Tuberculin Preparations of Klebs ... ..	177
(8) Béraneck's Tuberculin (TBk) ... ..	178
(9) Carl Spengler's Treatment with Bovine Tuberculin ... ..	180
(10) Other Tuberculins on the lines of Koch ... ..	184
(11) Active Methods of Immunization on the lines of Jenner and Pasteur ... ..	197
(12) Nastin and Tuberculo-Nastin ... ..	205
(b) Preparations designed to produce Passive Immunity... ..	208
(13) Maragliano's Serum ... ..	209
(14) Marmorek's Anti-tubercular Serum ... ..	211
(15) Hoechst Tubercular Serum ... ..	214
(16) Streptococcus Sera ... ..	216
(c) Vaccine Treatment ... ..	218
(d) Carl Spengler's Treatment with Immune Blood (IK) ... ..	218
<b>B.—SPECIAL SECTION</b> ... ..	223
1.—PULMONARY TUBERCULOSIS ... ..	224
2.—TUBERCULOSIS OF THE RESPIRATORY TRACT ... ..	234
3.—TUBERCULOSIS OF THE DIGESTIVE ORGANS ... ..	241
4.—TUBERCULOSIS OF THE UROGENITAL ORGANS ... ..	242
5.—TUBERCULOSIS OF THE SEROUS MEMBRANES ... ..	249
6.—TUBERCULOSIS OF THE EYE ... ..	250
7.—TUBERCULOSIS OF THE EAR ... ..	257
8.—TUBERCULOSIS OF THE SKIN ... ..	257
9.—TUBERCULOSIS OF THE GLANDS, BONES AND JOINTS ... ..	261
10.—TUBERCULOSIS IN CHILDHOOD ... ..	269
<b>Conclusion</b> ... ..	275
<b>Literature</b> ... ..	295
<b>Index</b> ... ..	303
<b>Plates and Temperature Charts.</b>	



## Introduction.

---

STATISTICAL inquiries as to the causes of death within the German Empire have shown an undoubted decrease in mortality from tuberculosis. In the "Medical Statistics of the Imperial Board of Health" the following figures are given on the point: In places in the German Empire with 15,000 and more inhabitants, the mortality from pulmonary and other forms of tuberculosis amounted in the year 1905 to 222·6 per 100,000 inhabitants; in 1906 to 202·7; 1907 to 197·7; 1908 to 192·45; 1909 to 182·6; and 1910 to 177·8. So that during the six years 1905-1910 there is an unmistakable, steady and considerable decrease in the numbers of deaths from tuberculosis among the urban population of about 300 of the largest places in the German Empire.

In the urban and rural population of twenty of the States of the German Empire, which are inhabited by more than 97 per cent. of the total population of the Empire, there died from tuberculosis per 100,000 inhabitants: In the year 1905, 205·7 (179·7 of these from tuberculosis of the lungs); in 1906, 188·2 (162·9); in 1907, 184·3 (159·6); in 1908, 178·6 (154·1); in 1909, 169 (145·3); and in 1910, 164 (140·5). Here also there is an appreciable decrease in the last three years, which is seen still more clearly in the actual figures: 1905, 120,338 deaths from tuberculosis; 1910, 102,761; therefore about 17,500 fewer victims. Further, the classification of these deaths according to the age of the deceased shows that tuberculosis has decreased both among persons at the most virile time of life and amongst children. Of 100,000 between the ages of 15 and 60 there died of pulmonary tuberculosis in 1905, 237·6, and in 1910, 191·6; between the ages of 1 and 15, in 1905, 52·1; in 1910, 36·1.

In Prussia, according to the "Medical Statistical Information of the Royal Prussian Statistical Authorities," there died from tuberculosis in 1910, 60,479 people, against 60,871 in 1909, 63,320 in 1908, and 65,054 in 1907. The figure per 10,000 of population for 1910 is just one half that for 1878 (the highest



point), and is the lowest yet recorded. The decrease, too, in the actual number of deaths (88,283 in 1886, to 60,479 in 1910) is all the more noteworthy in view of the increase of population from twenty-eight to forty million. Tuberculosis has decreased both in the country (46 per cent.) and in towns (48 per cent.). Of 10,000 children in Prussia between the ages of 1 and 15 there died from tuberculosis in 1876, 8.52; in 1910, 7.34. A decrease in infantile mortality from tuberculosis cannot therefore be recognized.

Lastly, a comparison of the number of deaths from tuberculosis before and after the year 1905 gives us the pleasing information that, after an increase of mortality in the year 1905, the death-rate from tuberculosis in the German Empire has now reached the minimum of all observations.

We must then examine the causes to which the marked decrease in mortality from tuberculosis during the last four years may be attributed. For in previous years the figures for tuberculosis had only shown slight fluctuations, and in 1905 even a slight increase. Undoubtedly many and various causes are here at work, and to go into all these would overstep the limits of this introduction. We would only draw general attention to the fact that the repeated and considerable decrease in the number of deaths from tuberculosis, which previously tended to remain stationary or even to increase, coincides in point of time and continues concurrently with the wider adoption of the specific treatment of tuberculosis. Whether this is the real cause or not, we will not at present discuss.

But, in spite of this decrease, we must not be satisfied and must remain convinced of the necessity for further prophylactic and therapeutic measures. For at the present moment in Germany the number of persons suffering from tuberculosis of the lungs is still to be estimated at about three-quarters of a million, and in Prussia the number of deaths from tuberculosis exceeds the total number of deaths from typhoid, diarrhoea, small-pox, scarlet fever, diphtheria, measles, whooping-cough, and puerperal fever by 50 per cent., while the death-rate from tuberculosis in children has scarcely shared in the fall of the total mortality from the disease.

It appears doubtful whether we doctors have much more that is new and important to say to the general public in order to enlist and retain its services in all classes on behalf of prophylaxis in tuberculosis. But the profession itself and the generation of practitioners now growing up may be enabled to get a more hopeful perspective of the disease, and to accomplish more than



mere symptomatic treatment. The whole modern campaign against disease is dominated by the endeavour to improve the methods of diagnosis on the one hand, and to make them accessible to the practitioner on the other. The campaign against tuberculosis also stands or falls with this improvement in diagnostic method, with the early recognition of the disease.

We must therefore pay the fullest attention to every practicable extension of diagnostic method, all the more as there is still no superabundance of available and trustworthy means for the early diagnosis of tuberculosis. In spite of all the progress made during the last two decades, tuberculin is still the sharpest and finest test for tuberculosis. But the last few years have given an entirely different aspect to the specific diagnosis of tuberculosis, although the optimism with which at first the universal value of local tuberculin tests was proclaimed could not be maintained. After a flood of publications, a broad and sure foundation has been laid from which basis the importance and due limitation of the various tuberculin tests can be defined, together with their indications and contra-indications.

We are free from that conservative standpoint which held fast to the old method—the test tuberculin injection of R. Koch—merely because of its age, its history, and its proved safety, though in diagnosis, if anywhere, the motto holds that the good must not be lost in striving to attain the better. It is from this standpoint that we have worked for years at the theory and practice of the treatment of tuberculosis. We have made numerous comparative experiments to test the various methods one against another, and to ascertain the limits of their applicability.

That the early diagnosis of tuberculosis is of the greatest importance from a hygienic and social point of view is now recognized by doctors and public officials everywhere and is considered as a fundamental fact confirmed and indeed proved by experience. But to us doctors a second fact is evident, namely that the timely recognition of pulmonary tuberculosis, whose frequency places it in the forefront of the various forms of the disease, is often fraught with such difficulties that physical diagnosis alone is at times impossible and must be supplemented by the specific methods of examination.

Doubts as to the value and success of sanatoria, which are still voiced here and there, can only be satisfactorily silenced by indisputable statistical proofs. In the first place it must be proved that the patients treated in the sanatoria, and on whom the statistics are based, are all suffering from *tubercular* pulmonary disease. But in the initial stage of tuberculosis this proof is



often only possible by means of tuberculin diagnosis. This is true in a still higher degree in the case of tuberculosis among children. "Only by the employment of tuberculin diagnosis are we able to distinguish those children who are suffering from tuberculosis from those who have fortunately escaped this disease" (Schlossmann, *Münchener med. Wochenschrift*, 1909, No. 8).

The earlier tuberculosis is recognized, the more easily and certainly is it curable. Confirmation of this statement is especially forthcoming in the reports of the principal sanatoria. Therefore the Berlin clinician Kraus considers it the duty of practitioners to make the fullest use possible of tuberculin in the diagnosis of cases where tuberculosis is suspected. On the other hand, at the Sixth Annual Congress of Sanatorium Doctors at Düsseldorf in 1911, objection was taken to the use and utility of tuberculin diagnosis in adults in ambulant practice. Our belief is that the demands which are being made at the present day are neglected or under-estimated. Tuberculosis must not only and primarily be diagnosed in adults, but also in children, and the diagnostic use of tuberculin by the subcutaneous method is even more urgently needed in sanatoria and hospitals than in ambulant practice. Our views on the matter were clearly voiced by Brecke at the same Congress: "If, as is demanded by the fight against tuberculosis and by the insurance offices, as many cases as possible shall be diagnosed at the beginning, Koch's test cannot be dispensed with" (Third Supplement to the "*Beiträge zur Klinik der Tuberkulose*").

Those connected with sanatoria are coming more and more to the conclusion that if not merely early cases of pulmonary tuberculosis are to be admitted, but cases in the second stadium, or even the more promising cases in the third, and permanent results are to be looked for, the hygienic-dietetic plan of treatment must be supplemented in some way; and it seems as if this can only be done successfully by means of specific treatment. Thus the latest reports of the German Central Committee for the Prevention of Consumption state that 70 per cent. of all institutions treating pulmonary tuberculosis employ tuberculin. For the real public sanatoria, Muttray gives the figure as 91 per cent. Some doctors at the public sanatoria even go as far as Ritter and prescribe specific treatment as a matter of routine just as they order relative amounts of rest and exercise.

Ritter, in his sanatorium at Edmundstal, first selected cases for tuberculin treatment which had been excluded from the public insurance institutions as being in too advanced a stage of tuber-



culosis, or which had already undergone treatment without avail. The results in these cases, which were far better than in those treated without tuberculin, converted him and made him an adherent of specific therapy. Ritter therefore holds that sanatorium physicians are not merely justified, but in a certain sense bound, "to make the widest possible use of tuberculin in the treatment of pulmonary tuberculosis" (*Deutsche med. Wochenschrift*, 1908, No. 29). A purely objective estimate of its value is furnished by the relative number of tubercle bacilli in the sputum. We will refer to the detailed statistics of Bandelier, Curschmann, and Löwenstein in another place. Here let the general statement suffice that under the combined sanatorium and tuberculin treatment at least twice as many patients lose their bacilli as under the hygienic-dietetic treatment alone. Even apart from the slight cases where, as Curschmann rightly states, the results are difficult to estimate, and considering only the results in the third stadium with and without tuberculin, the figures speak clearly enough: 12·1 per cent. of good results without tuberculin, 37·8 per cent. with tuberculin, and 42·1 per cent. with a protracted course of tuberculin. Curschmann therefore considers it quite justifiable to treat every suitable case with tuberculin from the first. "The patient is certainly not harmed, and he may reap great benefit."

The heads of private sanatoria in increasing numbers are also acknowledging their belief in the use of preparations of tuberculin in suitable cases. They recognize the "really definite benefits" of tuberculin treatment, and acknowledge the improved results in the treatment of progressive phthisis when tuberculin is added to the hygienic-dietetic method, especially as regards loss of fever and bacilli in the sputum.

Philippi, of Davos, noticed that in cases of fever treated specifically 72·2 per cent. lost their fever: of patients seriously ill in the third stadium, 70 per cent. lost their fever with tuberculin, and 45·8 per cent. without tuberculin. Janssen reports from the Deutsche Heilstätte in Davos extraordinarily clear cases of loss of fever due to tuberculin. Our own results are recorded later.

And the "financial" supporters of the treatment of tuberculosis follow the physicians in their appreciation of the specific treatment. Thus the public insurance office at Berlin has just fitted up a building for treatment with tuberculin where, after dismissal from the sanatoria, insured persons who are still not healed may get periodical out-patient treatment with tuberculin until they are finally cured. This combined system of treatment



with tuberculin in sanatoria and subsequent ambulant treatment has been worked for years by the public insurance institutions of West and East Prussia with the best results. It has now also been introduced by the management of the State Railways of Prussia and Saxony, who have their physicians specially trained in the specific treatment of tuberculosis.

Hospitals and infirmaries, too, in which tuberculin preparations have hitherto been very little used, are tending more and more to make use of specific treatment. We will quote here in the first place the words of Lenhartz, who proclaims in no uncertain voice the new era of tuberculin for hospital practice: "It is a serious omission to exclude the use of tuberculin" (Discussion on Ritter's paper, read before the Hamburg Medical Association, February 4, 1908). v. Leube repeatedly emphasized "the good results of sanatorium treatment, especially when combined with the use of tuberculin in the initial stages of the disease" (*Zeitschrift f. Tuberculose*, vol. 13, No. 5).

De la Camp, whilst laying great stress on hygienic-dietetic measures inside and outside the sanatoria, expresses himself in favour of tuberculin therapy extending over a long period (Session of the Upper Rhine Doctors, July 2, 1908). And according to Schlossmann, tuberculin is not only the best diagnostic, but also the best therapeutic means of fighting tuberculosis in children. Even in 1909 Schlossmann wrote: "To-day we already undoubtedly stand, and not in Germany alone"—as the two English, two French, Italian, Japanese, Portuguese, Russian, and Spanish translations of this text-book prove—"in the midst of a new era of the specific treatment of the initial stages of tuberculosis; and this era will, in my opinion, bring to tuberculin the recognition which, much to the prejudice of many an invalid, has been so long denied it" (*Deutsche med. Wochenschrift*, 1909, No. 7).

More were won over to this opinion by an inquiry set on foot by the *Medizinische Klinik* in 1910, as to the value of tuberculin in the treatment of pulmonary tuberculosis. The following extracts from the answers sent in by individual clinicians clearly show the revolution that has taken place in the opinion held as to the therapeutic power of tuberculin. (*Med. Klinik*, 1910, Nos. 1, 5, and 10.)

Fr. Kraus, of Berlin, writes: "In the first place it must be agreed that tuberculin treatment has not only been revived here and there, but is being universally applied in general practice. Tuberculin treatment must not become the affair solely of specialists."



N. Ortner, of Innsbruck : " I have never ceased to use old tuberculin in small doses and in carefully increased quantities, specially in afebrile cases of initial pulmonary tuberculosis, a proof that from my own experience I considered and still consider it a valuable remedy in the treatment of such cases."

Hirsch, of Gottingen : " With all three kinds of tuberculin (Koch's, Béraneck's, and Rosenbach's) we have seen good results to which no exception could be taken, in a series of carefully selected cases, and with very circumspect administration."

v. Leube, of Würzburg : " I therefore consider the treatment of pulmonary tuberculosis with small doses of old tuberculin as a therapeutic measure which undoubtedly favourably influences and effectively assists the usual treatment."

Moritz, of Strassburg : " In my opinion very good results may be obtained by treatment with old tuberculin. (I have no experience of any but this preparation.) I have seen good results both in pulmonary tuberculosis, not only in initial but also in advanced cases, and also in laryngeal tuberculosis."

Fr. Müller, of Munich : " In the course of the last eighteen years I have seen a whole series of cases of tuberculosis, in which, after treatment with tuberculin, quite striking improvement has taken place and apparently also a healing of the tubercular disease. I am speaking not only of tuberculosis of the lungs, but also of the peritoneum, the urogenital apparatus, and the eye. These results have led me to use tuberculin very widely in cases in the initial stage and where the disease is not very far advanced."

Heubner, of Berlin : " On the other hand I have used tuberculin for many years, always in small doses, in the glandular tuberculosis incipiens of children. Here the immediate beneficial effect of a careful treatment continued for about two months both on the general health and on the so-called scrofulous symptoms cannot be denied."

v. Stark, of Kiel : " In some cases an extraordinarily good subjective condition was noted in the days following the injection, which, in children, for instance, could not be attributed to the influence of suggestion; in such cases objective improvement also took place. Harmful effects were not observed. Without the aid of tuberculin we get splendid results in initial cases. . . . Nevertheless, I would not like to give up using it. Its administration in advanced pulmonary tuberculosis is permissible if used cautiously and with careful selection of cases, and sometimes gives good results."

Schultze, of Bonn, and Soltmann, of Leipzig are more



reserved as regards tuberculin, if not inclined to reject it. The former, in consequence of very good results from the use of tuberculin in tuberculosis of the eye, has lately taken up tuberculin treatment again. However, he reserves his judgment, but recommends a more extensive treatment of surgical tuberculosis with tuberculin as very desirable. Soltmann gives his experiences in clinically demonstrable initial pulmonary tuberculosis in childhood, in which with very small doses of old tuberculin he had no satisfactory results. For the rest he states very clearly, "I do not consider myself an opponent of tuberculin treatment."

Only Eichhorst, of Zürich, after experiments with Koch's old tuberculin, denies that there is any favourable healing action even at the very commencement of tubercular changes in the lungs: "My results were no different from those attained without tuberculin treatment by care of the body, good food, and suitable residence in the mountains, or even by a rest cure in an institution on some lower level."

In answer to the statement of Soltmann and Eichhorst we should like to say that on the one hand infantile pulmonary tuberculosis, when it is clinically manifest, is too unfavourable in prognosis, and on the other hand the very first beginning of tubercular changes in the lungs in the case of adults admit of too favourable prognosis for it to be possible to estimate correctly the therapeutic effects of tuberculin by them. But even if we only count the verdicts returned, we get as a result of the inquiry that of the eleven directors of university clinics, including children's clinics, eight are in favour of tuberculin treatment, only one against it and two undecided.

This also corresponds with the general impression made by the debate on "The Specific Diagnosis and Treatment of Tuberculosis" at the Twenty-seventh Congress on Internal Medicine at Wiesbaden in 1910. Penzoldt, who opened the debate, declared himself a convinced believer in tuberculin diagnosis and therapy, and in the course of the discussion Jochmann, Petruschky, Schlossmann, Sahli, Stintzing, Ed. Meyer, Rothschild, Jessen, Meinertz, Burghardt, Clemens, Romberg, and others did the same. The Prague clinician v. Jaksch alone expressed himself as against all employment of tuberculin, because there was absolutely no certain proof that "tuberculin has a specific effect," and because the combination of hygienic-dietetic treatment with the climatic influence of the South sufficed to cure. We are of opinion that there has never been any lack of strong and unmistakable proofs of the specific effect of tuberculin. The whole of the first tuberculin era is a chain of proofs that its specific effect was too powerful. On



the other hand, the treatment of such a disease of the masses by ordering patients to the South would meet with just as insuperable difficulties as the limitation of cures to high mountain districts.

Such Utopian proposals only serve to confirm what the president of the Congress, held at Wiesbaden two years ago, gave as the most noteworthy result of the prolonged debate on tuberculin: that the change in the value attached by clinicians to tuberculin was very apparent, as shown by the proceedings of the Congress on Internal Medicine in 1891, and now in the debates of the same Congress in 1910. The adhesion of quite an overwhelming majority of German clinicians to the claim of Koch for a specific diagnosis and treatment of tuberculosis is an accomplished fact. The same holds good in other countries; we will here only mention the warm recommendation of tuberculin treatment by Doyen, Mantoux, Mayor, Rénon, and others at the Eleventh French Congress of Internal Medicine (Paris, October 13-15, 1910), and the reports of the English clinicians, Grace Calvert, Eyre, Butler-Harris, Hewlett, Carmalt Jones, Latham, Lawson, Walters, and others. Radcliffe's statistics state that 20 to 25 per cent. of cases lost their bacilli with clinical treatment, 50 per cent. with combined tuberculin and clinical treatment (figures which exactly correspond to observations made in Germany).

In general practice, too, the time is past when the mention of tuberculin was taboo. After the unhappy experience of the first tuberculin era of 1890-91, with its unenlightened and mistaken method of administration, it certainly seemed advisable to leave specific diagnosis and treatment to those specially concerned with tuberculosis, and to limit its application to the sanatorium; and even later than this the question was rife whether it was advisable to place such keen weapons as the specific tuberculin preparations in the hands of uninstructed practitioners. To-day our position must be a different and a wider one. The specific diagnosis and treatment of tuberculosis are matters which have been closely investigated, and in some degree settled, since the value and freedom from risk in the administration of many preparations of tuberculin are well recognized, granted correct dosage and selection of cases. We can, therefore, to-day, without fear of catastrophes, recommend the specific treatment of tubercular disease to general practitioners.

If we aim at mastering tuberculosis, no matter by what means, the struggle must in the future be fought to an issue within the domain of the general practitioner. At present, with regard to



tubercular patients, the practitioner stands in an unsatisfactory position of too great passivity.

Non-specific drug treatment has failed, and can only bring amelioration of certain symptoms of the disease without stopping them at their source, even though any number of new and original "cures" are put on the market by enterprising firms. The same applies to the prescription of the ordinary six weeks' treatment at baths or mineral springs; and the hygienic-dietetic treatment, which produces good results in the sanatorium, meets in practice with insuperable difficulties chiefly on social and economic grounds. There remain the remedies with specific action, which, just because they do act specifically, allow no routine prescription and application.

Herein lies the difficulty for the busy practitioner, but one which can in truth be overcome by everyone, since it should stimulate him to make out of the practice of his profession what it properly should be: an art—the art of helping. Conflicts of interest are not to be feared: a fact of some practical importance. It will fall to the public or private sanatorium to prepare the tubercular patient by means of the hygienic-dietetic course, physically and mentally, for specific treatment, to initiate this treatment and get it past the greatest difficulties. The practitioner should be able to bring to a successful conclusion at home the tuberculin treatment begun in the sanatorium, since the period of treatment in the sanatorium, especially in the more severe cases, does not suffice to attain the utmost available improvement. In exceptional cases, one may be able to dispense with the after-treatment, or even with the preliminary sojourn in a sanatorium.

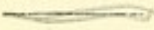
In any case the practitioner should become vanguard and rear-guard in the campaign against tuberculosis by means of specific diagnosis and treatment, and be able to follow with greater activity and satisfaction the fate of his tubercular *clientèle* than heretofore. Most important of all, the tubercular patient, thanks to the specific diagnosis of the practitioner, would reach the sanatorium in good time, and in case he be obliged to leave again too soon, would, thanks to specific after-treatment, be really cured. To wait for further experience or other specific remedies is no longer necessary. The remedies and the experience we have, and the patient has a right to have his disease recognized in good time, and so to be timely and successfully treated.

It is a question whether the generality of practitioners are ready for such a systematic task, but the signs of the times suggest it; and it is well that it is so, for it is the attitude of the practitioner that will decide whether the treatment of tuberculosis is to remain



a common object of practice or, outside the walls of the sanatorium, be confined exclusively to the consulting-room of the specialist.

There exists the need of accurate and good instruction in this specific method of diagnosis and treatment. The seventh edition of this book in five years bears witness to this. Opportunity to diagnose and treat tuberculosis with tuberculin is certainly at hand; for the student in his university, for the house-physician in his wards, and for the physician in his practice. But the highest degree of certainty and success in this direction will only be obtained by serious study, and to this end the following pages are devoted.





## I.—Theoretical Part.

---

EXPERIENCE has proved the victory of tuberculin as a diagnostic and therapeutic agent in the fields both of experimental research and of clinical investigation. To-day we know that the original conception of its discoverer, Robert Koch, of the nature of tuberculin action and reaction was based on a false foundation. The failures of the first tuberculin era can be traced to this misconception. With increased knowledge of suitable methods of administration and with the improvement of results, the need arose of understanding the phenomena which occur, of explaining the causes underlying them, and of applying the knowledge gained to the further development of the treatment. Thus in course of time there arose a number of theories to explain the action of tuberculin which differ from each other in many and important details, and of which many are still unrefuted and unreconciled. The views as to the explanation of the elective action of tuberculin on the tubercular process and the specificity of the tuberculin reaction are especially contradictory and different. These disagreements are emphasized by sceptics and critics, who argue that they go to prove the absence of specificity in tuberculin action. In discussing the most important of these theories we must acknowledge that we still lack a really satisfactory explanation of the physiological events in tuberculin action. But we hope and expect to interest the practitioner in the theory of the subject, because it helps to simplify and deepen the understanding of many a clinical fact in diagnosis and treatment, and because it probably forms a basis starting from which future research will reach the goal.

The most important theories of the tuberculin reaction will first be discussed, and secondly the curative action of tuberculin. In this we shall make use both of our own work and the most important results of research in the study of immunity [1]. In the arrangement of the matter we follow the method of F. Meyer [2].



## A.—Theories of Tuberculin Reaction.

---

### 1.—CHANGES IN THE TOXIN-SENSITIVE CELLS.

**Koch.** IN his classical studies on tuberculosis, Koch noticed the cellular changes following a tubercular infection. He writes [3]:—

When a healthy guinea-pig is inoculated with pure culture of tubercle bacilli the wound usually closes up and seems during the first few days to heal up. But in about ten to fourteen days there appears a hard nodule which soon breaks down, forming an ulcer which persists till the death of the animal. But the result is quite different when an already tubercular animal is inoculated. The most suitable animals are those which have been successfully infected some four to six weeks previously. In such animals the wound also heals at first, but forms no nodule, and on the following or second day peculiar changes take place at the site of inoculation; it becomes hard and assumes a dark colour, not limited to the site itself, but spreading to the surrounding tissue to a diameter of 0.1 to 1.0 cm. During the next few days it becomes clearer and clearer that the changed skin is necrotic; it is eventually shed and there remains a flat ulcerated area, which usually heals quickly and lastingly without infecting the neighbouring lymphatics.

**Buchner.** After Koch came Buchner [4], who came to much the same conclusions as we hold to-day:—

In order to give it a designation, we can for the present define this condition (after recent infection) as latent irritation caused by the tubercle bacilli present in the body. Of the latter there must always be a proportion which encounter unfavourable conditions for life and will degenerate and die, when their proteins will be set free and become active. The latent irritation caused by this is in its nature not a passive condition, but the expression of a reaction of the tissue elements, by means of which the latter attempt, although unsuccessfully, to free themselves from the exciting cause of infection.

Buchner, too, drew attention to febrile symptoms as a sign of tuberculin reaction.

Then followed the further observation that the same phenomena as appear after the re-injection of living and dead bacteria can be produced with their extracts—tuberculin. R. Koch was again the first to give details of this, but it remained for the later researches in immunity to separate the general from the cellular



reactive processes in the general changes occurring in the tubercular organism.

**Wassermann's  
Theory.**

The greatest notice, although criticism was both favourable and unfavourable, was taken of Wassermann's ingenious theory of the occurrence and absence of the tuberculin reaction. With the help of fixation of complement, Wassermann and Bruck [5] succeeded in proving the presence of dissolved products of metabolism of the tubercle bacilli and of their antibodies (anti-tuberculin) as reaction-products in extracts of tubercular organs prepared by trituration.

These antibodies, by virtue of their avidity for combination with antigen, extract the whole quantity of tuberculin injected from the blood and concentrate it in the tubercular focus. In the union of the antigen (tuberculin) with its antibody (anti-tuberculin) complement is fixed; consequently there takes place in the tubercular focus an increase of those elements (leucocytes, ferments) which possess protein digesting properties, leading thus to softening of the tubercular tissues.

This is the chain of events in a tuberculin focal reaction; it is usually accompanied by fever, which is then the result of the absorption of softened tubercular tissue.

**Christian and  
Rosenblat's  
Experiments in  
Fixation of  
Complement.**

Wassermann's theory is corroborated by the observations of Christian and Rosenblat [6], at Rubner's Institute: they found that in tubercular animals which have been injected with tubercle-bacillary preparations, an increase of antibodies causing fixation of complement and simultaneously a rise of the agglutinating power of the blood takes place.

While the agglutinins of tubercle bacilli, which are not identical with the antibodies, arise in the normal cells of the hæmatopoietic organs, the complement binding "tubercular" antibody is exclusively formed in tubercular tissue. The occurrence of these bodies in the serum does not produce immunity from tuberculosis, but is its sign.

This agrees with the fact that Wassermann, Bruck, Citron, Lüdke, R. Kraus and others also proved the presence of antibody in tubercular patients treated with tuberculin, the antibody causing fixation of complement in the serum and in the tubercular foci.

According to our own researches, this takes place frequently, but not always.

**Lüdke.**

This theory explains the reduced or even obliterated reactivity of the tuberculinized



organism, in spite of the presence of the disease: the absence of reaction is caused by the fact that anti-tuberculin is present in the serum and arrests the tuberculin before it can reach the focus of disease. The statements of Lüdke [7] bear this out: that reactivity to injected tuberculin is generally maintained when no anti-tuberculin can be found in the serum, and that conversely it is just in those cases where anti-tuberculin is proved to be present in the serum that the tuberculin injections are borne with little or no reaction.

**Bauer.** In addition, Bauer [8] found in his research in complement fixation in children's tuberculosis that with the appearance of a fair quantity of anti-tuberculin in the blood, the reactivity of the organism to cutaneous and subcutaneous tuberculin decreased.

In tubercular adults the antibody causing fixation of complement also appears spontaneously, *i.e.*, without previous specific treatment, in the serum and exudates. Since these observations of Wassermann, Citron, Bruck, Lüdke, Michaelis, Leonor, and Wolff-Eisner were made chiefly on cases with severe lesions and miliary tuberculosis, the absence of reaction to subcutaneous tuberculin in advanced cases is also intelligible. Antigen and antibody may unite in the serum and cause the neutralization of the tuberculin to take place in the blood, not in the diseased tissues; thus both local reaction in the focus of disease and general reaction are prevented. But even in cases not so far advanced, the "tuberculin-neutralizing antibodies" act upon the "hypersensitizing substance" and tend to prevent a tuberculin reaction. On this depends the necessity of individualizing the doses of tuberculin used for diagnostic purposes.

**Objections to  
Wassermann's  
Theory.**

The researches of Wassermann and Bruck and their bearing on the action of tuberculin have not remained uncontested. We may refer to the objections of Weil and Nakajama [9] and Morgenroth and Rabinowitsch [10], which, however, seem in the main unsound. The doubts they express as to the specificity of the antibodies in particular are shown to be unjustified by the serological investigations of Engel and Bauer [11] on children at the Düsseldorf Academy. They never found spontaneous antibodies in the blood of a tubercular suckling or young child—in contradistinction to the adult phthisical patient—never in healthy children, and never in cases of syphilis and pneumonia. On the other hand, antibodies were produced in the blood of all tubercular children by the injection of tuberculin, which attained the maximum



with the quantity of tuberculin injected, and after cessation of the injections disappeared again, first rapidly, then more slowly. From these facts we see that we are dealing with a specific deviation of complement, *i.e.*, with specific antibodies to tuberculin, as Wassermann and Bruck have maintained from the very first. The substitution of the term "anti-tuberculin" for "antibody producing fixation of complement," is quite immaterial; it is also immaterial that the amount of anti-tuberculin and the susceptibility to tuberculin do not necessarily run parallel. The specificity of the antibodies in tuberculosis is also proved beyond dispute by other authors, recently by Lüdke and Sturm [12], who both obtained diagnostic reactions in tubercular patients only by means of tuberculin preparations, never with extracts of streptococci, typhoid, dysentery, or colon bacilli.

**Citron's  
Modification.**

Citron [13] has somewhat modified and completed Wassermann's theory. He assumes that in the tubercular focus there are toxin-sensitive cells, which, by the injection of small doses of tuberculin, become rich in receptors (sessile receptors). The latter attract the injected tuberculin, produce the reaction, and are finally disposed of in the blood. Besides these cells in the foci, Citron holds that also all other cells in contact with tuberculin form these specific receptors, which are shed into the bloodstream. Thus in many cases, instead of neutralizing the tuberculin, they may produce hypersusceptibility to tuberculin; and this hypersusceptibility increases with the number of sessile receptors in the focus. Citron has also proved that such sera in conjunction with tuberculin and complement kill guinea-pigs. Thus the occurrence of hypersusceptibility to tuberculin after repeated injection of small doses is explained.

**Pappenheim.**

According to Pappenheim [14], neither the free nor the sessile receptors produce the phenomena of the tuberculin reaction, which are caused by the fresh formation of these receptors due to the tuberculin injection. According to this, the tuberculin reaction would be simply the active "anti-reaction" of the organism.

## 2.—THE TOXIN THEORY.

**Koch.**

The first to explain the tuberculin reaction as a toxic action was R. Koch [3] himself. According to his original description, tuberculin produced deep-rooted changes in the nutrition of the tubercular tissue, causing its destruction. The toxic process is accompanied by fever and general reaction. On healthy people, the toxin only acts



in relatively large doses. The same was found in animal experiment: 0.5 c.c. old tuberculin kills a tubercular guinea-pig, while a healthy animal tolerates this dose without reaction. Thus Koch saw in tuberculin a true toxin, which by injection in slowly increasing doses is capable of producing immunity. When the doctrines of immunity were subsequently revised and extended, he changed his ideas, inasmuch as he considered tuberculin treatment an active immunizing process.

**Hertwig.** Almost greater attention was paid at the time of its description to Hertwig's toxin theory, which, influenced by Metchnikoff's phagocyte teaching, explained the tuberculin reaction as a primary focal reaction produced by a chemotactic influence of the leucocytes. Hertwig [15] based his theory on Stahl and Pfeffer's laws of chemotaxis; he considered that the leucocytes of a tubercular organism, by virtue of the continual production of toxin in the foci, became tolerant of the tuberculin, and that after an injection of tuberculin a positive chemotactic irritation is exerted on the leucocytes previously at rest owing to the increased concentration of the tuberculin. This influx of leucocytes causes the focal reaction, on which the febrile and general reaction is dependent.

**Ehrlich.** Ehrlich [16] localized the reaction in the middle of the three cell layers which encircle the tubercular focus like the layers of an onion. While the central caseated and the adjoining normal tissues were undamaged by tuberculin and insensitive to the toxin, the intermediate zone, damaged by the toxins of the bacilli, was specially capable of reaction. The production of specific antibodies took place in these toxin-sensitive cells; and the production of antibodies was the essential part of the mechanism of the reaction.

**Tuberculin a Primary Toxin for the Tubercular Organism.** Of late the standpoint has been increasingly taken up that tuberculin is a primary toxin for the tubercular organism, chiefly because there is no proof of the presence of an anaphylactic reactionary body, either by a serum reaction or by transference of hypersusceptibility (R. Kraus, Löwenstein, Volk, and others). It is now generally considered that there circulates in the tubercular organism a hypothetical antibody—Wassermann calls it anti-tuberculin, Wolff-Eisner an albuminolytic, Sahli a bacteriolytic amboceptor, Citron a sessile receptor—which changes the tuberculin, inert in itself, into a highly toxic substance. On this basis the tuberculin reaction is explained by assuming that the tuberculin set free in the focus first causes hyperæmia—focal reaction—



and from the resulting general intoxication the general reaction follows.

That tuberculin is a primary toxic tubercle "poison" is proved by the action of Landmann's [17] Tuberculol, of which a dose of 1 c.c. kills a healthy guinea-pig of 250 grm. weight. But tuberculin differs from the true primary toxins in that it is unable to cause formation of antibodies in a healthy organism. Nevertheless, the idea of a primary toxic action to explain tuberculin reaction is justified, as Pickert [18] and Löwenstein [19] proved in the serum of tubercular patients treated with old tuberculin the presence of specific substances (anticutins) which neutralize the action of tuberculin on the skin. The nature of these anticutins is at present quite unknown; their presence was also proved by Hamburger, v. Monti, White, Graham, and others. It is certain that, in addition, other antibodies may arise after tuberculin injections. Ruppel and Rickmann [20] have proved that the serum of immunized animals not only neutralizes tuberculin, but even renders tubercle bacilli non-toxic. And quite lately Abderhalden has shown that blood-plasma of tubercular patients, in contrast with that of normal individuals, can decompose peptone extracted from tubercle bacilli.

Meyer and  
Schmitz.

While Hertwig explained the tuberculin reaction on the basis of the condition of the leucocytes, F. Meyer and K. Schmitz [21] have recently found in the *red* blood corpuscles of tubercular animals a reactionary body, which, after corresponding combination with tuberculin, forms toxic substances. These authors explain the tuberculin reaction as follows: The injected tuberculin is taken up by the erythrocytes and carried to the focus, where the first and strongest receptors for tuberculin—the anti-tuberculin of Wassermann—are found. These receptors exert, after the injection, a great attractive irritation on the blood corpuscles containing tuberculin and thus cause the hyperæmia of the focus and the focal reaction. Simultaneously the toxin set free by the union of receptor with tuberculin causes the general reaction. The repeated injection of small amounts of tuberculin leads to the formation of increasing quantities of toxin, to which the body replies with insensitiveness, possibly brought about by formation of the antitoxins.

### 3.—THE AMBOCEPTOR THEORY OF WOLFF-EISNER.

Wolff-Eisner [22] modified Wassermann's observation by substituting for tuberculin the bacterial bodies or the fragments of



them contained therein, and for the antibodies (anti-tuberculins) the bacteriolysins present in all subjects of tubercular infection. The fragments of bacilli, as such, produce no result: the simultaneous presence of bacteriolysins "unlocks" them, setting free the potent substances they contain, and these act on the diseased focus and the body as a whole, producing the tuberculin reaction. In this connection hypersusceptibility plays a marked rôle. On it depends the mobilization of the bacteriolytic powers of the body, the condition of hypersusceptibility at the particular moment governing the grade of toxin production and absorption.

**Zieler.** According to Zieler [23], however, the idea of insoluble corpuscular fragments of bacilli, even if ultramicroscopic, to explain the action of tuberculin is untenable, since the dialytic products of tuberculin have the same action as old tuberculin and bacillary emulsion. Therefore the assumption of bacteriolysins for the occurrence of tuberculin action is untenable. Wolff-Eisner has now extended his conception, inasmuch as he now considers that the lytic amboceptors not only dissolve the bacilli, but also decompose the toxic bacterial proteins arising from them; the bacteriolysins are also albuminolysins.

**Sahli.** Sahli [24] agrees in general with Wolff-Eisner; he considers the lysinized tuberculin an active antigen, forming secondary endotoxin. On the other hand, F. Meyer [2] demands, for a

**F. Meyer.** satisfactory interpretation of Wolff-Eisner's theory, the proof of the lytic amboceptor in the serum of tubercular patients and the definite passive transference of hypersusceptibility. But the experiments of Ruppel already mentioned show, in opposition to these demands, that a tubercular serum with bacteriolytic properties is able to annul tuberculin action, not to increase it. Also the distinctly decreased power to cause reaction of sensitized tubercle bacilli in tubercular individuals speaks against the lysin theory, as on the latter the sensitization would cause considerably stronger reactions.

#### 4.—THE THEORIES OF HYPERSUSCEPTIBILITY.

The conception of hypersusceptibility is ascribed to v. Behring, but specific hypersusceptibility was first established by Koch himself by the discovery of two facts: (1) That tubercular guinea-pigs reply to a second infection by tubercle bacilli with necrosis and shedding at the place of inoculation, and (2) that only the tubercular organism exhibits a typical reaction to tuberculin.



Kretz [25] then proved that a normal animal does not reply to the injection of an equilibrated mixture of toxin and antitoxin with the formation of antitoxin, while a previously treated animal reacts to the same injection with a copious production of antitoxin. In consideration of this fact, Löwenstein and Rappaport [26] were induced to test the same chain of ideas, using tuberculin. By the repeated injection of the smallest doses of tuberculin, they succeeded in artificially producing a hypersusceptibility of the organism to tuberculin.

v. Pirquet's  
Allergia.

v. Pirquet [27] coined the word "allergie" to describe a changed capacity for reaction (*ἄλλη ἔργεια*). This idea of allergia has also been applied to the tuberculin reaction. Just as in animals which have undergone previous treatment with protein, so in the tubercular subject there is an allergical action against the bacterial protein. Thus the cutaneous tuberculin reaction also depends on allergia, *i.e.*, on the altered reaction which the organism gives to the infecting agent, already known to it. The person inoculated for the second time—or the tubercular individual—reacts in point of time, quality and quantity differently from one inoculated for the first time—or the non-tubercular.

As long ago as 1903, v. Pirquet and Schick had, on the occasion of the discussion at the Gesellschaft für Kinderheilkunde (Cassel, 1903), expressed the view that the capacity of the tubercular patient to react to tuberculin, of the vaccinated subject to vaccine, and of the animal inoculated with horse-serum to serum, were all conditioned by "reaction-products of the nature of antibodies." Further clinical investigations on the various forms of reaction to ordinary vaccine lymph led v. Pirquet to the observation that reaction only occurred within twenty-four hours in the case of previously vaccinated subjects, and that this capacity of "vaccinal early reaction" begins during the febrile period of vaccination and lasts several years.

An entirely analogous reaction of hypersusceptibility of the skin (*allergie*) he observed to occur when, in the tubercular subject, a small quantity of tuberculin was applied cutaneously. At the spot there developed in the skin a reaction remaining localized, an inoculation papule, also based on the principle of the vaccinal early reaction and conditioned by the coming together of toxin (tuberculin) and antibody. The presence of antibody demonstrated by the reaction affords proof of the existence of a previous or still active tubercular infection in the inoculated organism. This is, in its main features, the line of thought which led v. Pirquet to the diagnostic application of allergia in tuberculosis.

Friedberger.

The latest theory of hypersusceptibility is Friedberger's theory of anaphylaxis. The word "anaphylaxis" introduced by Richet is applied to the



phenomenon of hypersusceptibility which occurs after injection of solutions containing foreign protein, discovered by v. Behring some time previously. The change of terminology—hypersusceptibility to anaphylaxis—is rather unfortunate; for anaphylaxis denotes lack of protective power, while hypersusceptibility is almost the exact reverse. Friedberger [28] considers the hypersusceptibility the result of the anaphylatoxin arising by the action of antibodies from the foreign protein injected. According to his view, the tuberculin reaction takes place as follows: The antibodies formed by the tuberculin injection set free toxin from the tubercle bacilli in the focus, which cause the focal and general reaction. This hypothesis of hypersusceptibility to tuberculin is disputed by some authors. Thus Bessau holds that it is bound up with the tubercular inflammation, while the condition of reduced susceptibility to tuberculin is “non-specific” and to be considered as “anti-anaphylactic.” We hold that the lasting insusceptibility of specifically treated patients is an argument against Bessau’s interpretation and proves its real nature—a phenomenon of immunity. Friedberger and his co-workers object to the technique of Bessau’s experiments, in which the specific anti-anaphylaxis is only partially masked by non-specific resistance and, in a series of important researches [29], bring forward new experimental proofs which still further establish the doctrine of the specificity of anti-anaphylaxis.

**Objections.** Further objections have been made against the theories which give hypersusceptibility as the cause of the tuberculin reaction, of which the most important is that which urges that the passive transference of hypersusceptibility to tuberculosis in man or guinea-pig has hitherto proved impossible. Our own experiments in this direction have also all been negative. However, we ought not summarily to reject the connection between the tuberculin reaction and protein anaphylaxis. It is doubtless present in *allergia* in the sense of v. Pirquet, so that it can only be concluded that the subcutaneous and cutaneous reaction cannot be identified. Quantitative conditions, other unknown factors and also the immediate absorption and diffusion of subcutaneous tuberculin in the body may play a part.

It is also striking that the tuberculin reaction is accompanied by fever, while a *fall* of temperature is characteristic of hypersusceptibility. But this collapse temperature is not uniformly regular in its appearance. Friedberger and Mita succeeded in proving that, also in ordinary protein anaphylaxis, guinea-pigs react with fever to very small doses on the second injection.



And Bauer showed that the guinea-pig infected with tubercle bacilli does not always react with fever, but with some variation of temperature, sometimes above, sometimes below the normal; here, too, the small doses caused fever.

**Chain of Events in Tuberculin Action.** If we consider that we are dealing in human tuberculosis with a chronic infective disease, with frequent relapses and exacerbations, the following chain of events in a tuberculin injection given to a tubercular patient seems plausible. By the tubercular infection there arises a surcharge of bacterial protein from the tubercle bacilli; this incites the body, first locally and then in general, to the formation of digestive ferments and leads to the production in the blood of the patient of tubercular "anaphylatoxin." Now, with the tuberculin injection new foreign protein is introduced; as in ordinary protein anaphylaxis, this is decomposed by the anaphylatoxin and toxic antibodies are formed which have a harmful action on the cellular protoplasm, causing it to degenerate and soften. From this there result disturbances due to anaphylaxis or hypersusceptibility, as the expression of the tuberculin reaction. But while in ordinary protein anaphylaxis a fall of temperature is characteristic, owing to the large quantities of protein, in tuberculosis the reaction due to hypersusceptibility takes the form of tuberculin fever on account of the extremely small doses, thousands of times below the lethal amount. This event is accompanied on the one hand by a destruction of the bacteria, on the other by a neutralization of the toxins which circulate in the organism of the tubercular patient and thus result the improvement and sense of general well-being that we, in conjunction with F. Kraus, Saathof, Hager, Longard, and others, have so often observed to follow severe tuberculin reactions.

## 5.—THE THEORY OF NON-SPECIFIC ACTION.

**The Albumose Theory.** A certain number of authors ascribe the tuberculin reaction to the action of non-specific substances which pass into the preparation from the culture medium during the manufacture of the tuberculin. This brings us back to the old albumose theory advanced by Kühne [30], Matthes [31], and Krehl [32], according to which tuberculin action is explained in the following way: The tuberculin, which contains abundant albumoses, is, after injection, attracted to the albumoses in the diseased areas and



produces, wherever it meets with other albumoses, *i.e.*, in the tubercular focus, a local reaction; it also flushes albumoses out of these areas, causing a general febrile reaction. This explanation bears a close analogy to Wassermann's theory, but it takes no account of the differences between the albumoses and tuberculin already recognized by Zupnik [33] and Matthes and Krehl [32], differences which prove that tuberculin must contain something specific. For instance, in order to obtain a toxic albumose effect, much greater doses are necessary than are employed in the diagnostic use of tuberculin. This Krehl, Matthes, Béranek, Freymuth, and Landmann have pointed out. A tubercular animal which reacts with fever to 1 mg. old tuberculin, and to 10 mg. peptone, receives in the tuberculin injection 1/10 mg. of peptone, the hundredth part of the amount of peptone necessary to promote a peptone reaction. The final blow to the albumose theory is given by the fact that with albumose-free tuberculin prompt specific results can be obtained.

**Conclusions.** In reviewing the various explanations of the tuberculin reaction, Wassermann's theory still seems to have a satisfactory theoretical foundation. In strict contrast to the albumose theory, it asserts the specificity of the tuberculin reaction and of tuberculin itself, which has, moreover, been demonstrated by so many experiments that it must be looked upon as an axiom.

A further point is that specific hypersusceptibility has an application in harmony with the experience of tuberculin treatment. The constant and uniform factor in all tubercular subjects is the presence of antibodies, the variable factor through all shades of difference the hypersusceptibility. The latter is only the factor which determines the quantitative reactivity of the organism, while the qualitative factor is the presence of antibodies in the tubercular individual, be these designated anti-tuberculin, complement-fixing reactionary bodies, albuminolytic or bacteriolytic amboceptors, or sessile receptors. But at any rate the degeneration of the tissues themselves is a partial cause of the hypersusceptibility shown by the tubercular organism.

As far, then, as our present knowledge goes, the explanation of the specificity of the tuberculin reaction is essentially associated with the relations between the preparation of tubercle bacilli injected and the tubercular body or tissues saturated with antibodies. And these relations ultimately bring us back again to the phenomenon of hypersusceptibility, the laws of which are not yet fully defined.



## B.—The Curative Factors of Tuberculin Action.

---

### 1.—TOX-IMMUNITY.

**Disappearance of Subjective Symptoms ;** THE disappearance of reaction to tuberculin was originally interpreted by R. Koch as a sign of the complete healing of the tubercular tissue. To-day we know that this is not the case, and that tolerance of tuberculin is to be considered an immunization against a bacterial toxin, of which Koch founded the first example. The theory of antitoxins will be discussed later; here we shall consider immunization against tuberculin purely from a clinical standpoint. The systematic production of toxin tolerance and finally tox-immunity must offer advantages to the organism in its fight against the disease, as many of the general phenomena of tuberculosis are to be attributed to the absorption of the toxic substances from the tubercle bacilli. Now it is most striking how these subjective disorders or general toxic symptoms (such as headache, palpitation, pains in the chest, discomfort, restless nights, nervous irritability, loss of appetite and general weakness) very often quickly disappear under tuberculin treatment and are replaced by a permanent state of good health. It is also certainly advisable to immunize the patient against those quantities of toxin which he may often suddenly produce by unusual exertion (auto-tuberculin).

**of Dysmenorrhœa and Amenorrhœa ;** In this connection the observations of Hollós and Eisenstein, lately confirmed by Macht, deserve notice. They state that dysmenorrhœa and amenorrhœa in manifest and latent tuberculosis regularly disappear in many cases under tuberculin treatment.

According to this, tubercular intoxication seems to play an important part in the etiology of menstrual complaints; we can confirm both this conclusion and the favourable result of tuberculin treatment.

**and of Objective Symptoms.** Also the objective symptoms of similar origin (such as fever, night sweats, high pulse-rate, many pleural troubles, glandular swellings, &c.) generally subside more rapidly under tuberculin, whereas without it they belong to the more frequent complications of the many-sided clinical picture of the disease.



In some sanatoria the slight uncomplicated cases are not submitted to tuberculin treatment, but only the severe cases, in which the hygienic-dietetic method alone does not guarantee the highest possible degree of success. In such institutions it is a fact, evident not only to the doctors, but also to the patients themselves, that of those treated with tuberculin—all cases of open tuberculosis—it is seldom that a patient is confined to bed from any indisposition, while of the others, not treated with tuberculin, a certain percentage is regularly bed-ridden.

#### Value of Tox-immunity.

It has lately been asserted in many quarters, on purely theoretical grounds and in support of individual theories, that tox-immunity may not be to the advantage of the tubercular patient. We will mention, therefore, the experiments of Pickert [34], who draws attention to the fact, well known to all experienced tuberculin therapists, that patients whose disease takes a conspicuously favourable course possess a raised *natural* resistance to tuberculin, which speaks for a high resistance of the organism to the disease. This is reminiscent of the fact that we [35] discovered many years ago that a large percentage of slight cases of favourable tendency to heal, which were submitted to the hygienic-dietetic method alone, showed at the conclusion of treatment high tolerance of tuberculin, while, on admission, they were highly sensitive to small doses of tuberculin. From these results we can at once draw the conclusion that also an *artificially* acquired tolerance of tuberculin cannot be disadvantageous, but that we are undoubtedly on the right road in our therapeutic endeavours. It is our experience that just those patients who tolerate tuberculin well, *i.e.*, in whom it is easy to produce tox-immunity, progress favourably. The tuberculin tolerance is evidently advantageous; it is a sign that the diseased organism—of its own power, or aided by specific treatment, as the case may be—is repelling the toxic action of the tubercle bacilli, that it has acquired a relative tox-immunity. Our view, which has received confirmation year by year, is shared by many competent authorities; we will only mention Sahli and Much of the many authors who attempt to produce tox-immunity in their patients.

#### Two Forms of Insensitiveness to Tuberculin.

With increasing tox-immunity, the condition of insensitiveness to tuberculin can occur. We distinguish two forms, also recognized as such by Hamburger and Monti: (1) A forced incapacity to react; (2) a true immunity.

As the cause of the former—the insensitiveness of individuals treated for a long time with tuberculin—Wassermann [5] described the anti-tuberculin circulating in the blood. These amboceptors intercept the tuberculin, neutralize it, and prevent the



focal reaction, for which reason their occurrence in the blood is to be avoided. Therefore he claims that capacity for reaction should be maintained in tuberculin treatment. In spite of our complete acceptance of Wassermann's theory in itself, we cannot accept this explanation for reasons expressed by F. Meyer [2]: he was able to show that sera without complement-fixing antibodies could neutralize tuberculin *in vitro*; Citron proved that patients without antibodies may be insensitive to tuberculin; Weil and Strauss proved that susceptibility to tuberculin is independent of the content of complement-fixing antibodies in the serum; also according to Kretz's phenomenon, already mentioned, a fresh production of antibodies can occur in the focus in spite of apparent neutralization. It is, in addition, unintelligible that while the anti-tuberculin displays a neutralizing action in the serum, in the focus it is productive of reactions; according to Ruppel, the combinable amboceptors appearing after tuberculin injection may in animal experiment even exert a healing influence. Lastly there is the most important argument from a clinical point of view, and one we can ourselves confirm; it is just in patients with high antibody content and excellent general condition that unmistakable focal reactions can be observed after tuberculin injections.

Friedberger [28] and we ourselves, in antithesis to Wassermann, hold that the insensitiveness to tuberculin is a healing process caused by the curative action of the previously formed antibodies. At the commencement of treatment, these are but scanty, and therefore set free anaphylatoxin, evident in the form of hypersusceptibility; but later in a successful course of tuberculin they are increased, split up the tuberculin, and lead to insensitiveness.

**Roemer's  
Hypersusceptibility  
of Animals.**

Now as an argument against the advisability of producing immunity to tuberculin, the work of Roemer [36] has been quoted, who showed that animals hypersusceptible to tuberculosis may be immune to a fresh infection. Therefore it is argued that it is a mistake to render patients insensitive to tuberculin, and that, on the contrary, an effort should be made to increase their hypersusceptibility to tuberculin in order to protect them against re-infection. But "hypersusceptible to tuberculosis" is by no means identical with "hypersusceptible to tuberculin." Also, according to our experience extending over many years, the occurrence of hypersusceptibility in the course of tuberculin treatment has never been of advantage to the patient in question, and this is the view of other experienced tuberculin



therapists. On the contrary, we can point to a whole series of cases of open pulmonary tuberculosis clinically healed with large doses of tuberculin who after many years have remained cured, both as regards physical signs and working capacity, and have retained a relatively high tuberculin immunity—permanent cures of open tuberculosis without hypersusceptibility.

**Conclusions.** Opinions of the nature of hypersusceptibility are not yet fully clear: on this account we shall not attempt to explain the action of tuberculin on its basis nor draw conclusions from it with regard to the therapeutic employment of tuberculin. Only this much will be said: it does not seem to us admissible to quote the hypersusceptibility of initial cases of favourable prognosis as an argument for the maintenance or increase of the hypersusceptibility in tuberculin treatment. The favourable prognosis of such initial cases does not depend on the hypersusceptibility in itself, but on the smallness of the focus of disease. From a small focus there proceed only small quantities of antigen for absorption, so that the tubercular organism remains "hypersusceptible" for some time; this the more, the fresher the process of the disease. Also, although it is very generally done, it is certainly incorrect to apply the terms "high susceptibility to toxin" and "cumulative surcharge of toxin" without differentiation; these biological reactions are no more identical than the insensitiveness to tuberculin due to saturation of the antibodies or absence of power to react, and the immunity to tuberculin as a sign of true antitoxic immunity to the toxin of tubercle bacilli.

## 2.—THE FOCAL REACTION.

### Local Hyperæmia.

The second specific factor in tuberculin action is the local hyperæmia, most clearly seen in reacting lupus tissues. The inflammatory hyperæmia and the increased flow of serum form the anatomical basis for the action in the diseased tissue. The same hyperæmia is here at work as a healing factor whose importance in bacterial infections has been specially pointed out by Buchner, and whose practical application for almost every kind of inflammation in the most varied diseases Bier has described as "the most general and extensive healing method extant." The extremely favourable results in the tuberculin treatment of tubercle of the iris are a strong witness for the therapeutic significance of hyperæmia produced by tuberculin; it is just in the highly vascular tissue of the iris that a large degree of hyperæmia and



copious saturation with serum can be produced by the local reaction. And on the other hand histological experiments in lupus have shown that local reactions do not occur when the tubercular foci are excluded from the circulation by reason of fibrotic changes. Neither in such places nor in their neighbourhood does the staining of serial sections reveal the presence of vessels. The tuberculin is deprived of the possibility of reaching the foci (Klingmüller [37]).

**Results of the Hyperæmia.** The action of hyperæmia and inflammation is a double one: on the one hand absorption, on the other demarcation, softening, necrosis, and extrusion. Virchow has justly demanded a more precise use of the term "tubercular tissue," a differentiation between the tubercle, the tubercular ulcer destined to break down, the true tubercular tissue, and the purely inflammatory changes of the tissues adjoining the tubercle, in which latter tuberculin displays its action. Thus tuberculin action must be described as follows: In the first place, general infiltration of the diseased tissue with blood and blood cells; then with decreasing hyperæmia, washing out of the inflammatory elements into the blood and lymph channels, and by repetition of this, gradual complete absorption; finally, in all situations where the tubercular changes in the tissues are so far advanced that absorption is no longer possible, softening and disintegration.

### 3.—THE ANTIBODIES AS CURATIVE FACTORS.

#### (a) Antitoxins.

**Löwenstein and Pickert.** Löwenstein [19] and Pickert [18] have proved beyond question that true antitoxins occur in the blood of tuberculin-treated patients. The capacity for antitoxin formation is not developed to the same extent in all tubercular subjects; where the disease has taken a fibrous character, antitoxin is formed most readily. To obtain immunity, comparatively large quantities of antigen are essential; antitoxins are most easily found in highly immunized patients. The increased value of a serum does not depend so much on the fact that the same quantity of serum can neutralize a larger quantity of tuberculin, but that the mutual avidity of antibody and antigen is increased, and the strength of the newly established combination is greater.

From the results of these researches, Löwenstein concludes that the antitoxins probably play an important part in the healing



process of tuberculosis, especially when they are formed at an early stage in the disease.

**Ruppel.** Ruppel [38], in the Höchst tubercular serum (described later), has made a preparation on new principles of his own which allows the exact study of the properties of the serum of a specifically treated patient. In the serum of the immunized animals all known antibodies occur; it renders bacilli non-toxic, and displays a protective and healing action on guinea-pigs. Ruppel, too, explains the healing action by the content of antitoxins.

### (b) Agglutinins.

**Relation between Agglutinating Power and Immunity.** In the natural course of tuberculosis, no formation of specific agglutinins takes place. In the treatment of animals with bacterial cultures for immunization there appear in the blood both agglutinating and immunizing properties. Therefore Koch [39] thought the assumption justified that animals artificially raised to high agglutination values possess a certain degree of immunity against infection with tubercle bacilli. And, in point of fact, he obtained unquestionable proof of this. He inclined to the belief that the agglutinating property was part and parcel of the complicated entity of immunity. The animal experiments gave colour to the view that the height of the agglutination value stood in a certain relation to the immunity attained, and it became a question of reaching the highest possible agglutination values in man. This is most successful when an extremely fine emulsion of pulverized tubercle bacilli in physiological saline solution is employed for immunization.

**Agglutination Value in Tuberculin Treatment.** Arloing and Courmont had already succeeded, by injections of attenuated tubercle cultures, in increasing the agglutinating power in animals; up to 1:600 in a dog. Koch went further and obtained an agglutinating power of 1:3,500 in a donkey. The highest agglutination values noted by Koch with his method were 1:200 and 1:300, but his were for the most part severe cases. We have obtained values of 1:1,000 even with patients in Stadium 3. The outcome of these investigations [40] into the occurrence and significance of agglutination during tuberculin treatment can be stated as follows:—

(1) By treatment with bacillary emulsion the agglutinating power can almost always be raised.

(2) The better the prospect of improvement or recovery, the more rapidly the agglutinating power rises and the greater the extent and duration of the rise.

(3) The more unfavourable the outlook, the more difficult it is to raise



the agglutinating power at all and the more rapidly it is lost; persistence of a very low agglutination value denotes in general progressive disease.

(4) Determination of the agglutinating power, although of great value and interest, is not to be regarded as an essential factor in the technique of tuberculin treatment.

#### The Proper Place of the Agglutina- tion Method.

Hence when Koch writes: "The agglutination method places the means in our hands of making sure step by step whether we are on the right road with our attempts at immunization, and puts an end at one blow to the earlier uncertainty," the application is to immunizing processes in general, not to the treatment of the individual. For the agglutinating process is a valuable indication that by means of tuberculin treatment processes of a really specific nature are started in the body, and substances formed which possess a specific action on the protoplasm of the tubercle bacilli. From experience with other bacteria we know that the production of agglutinating substances takes place regularly in the process of immunity, and hence in the specific treatment of tuberculosis the phenomenon of agglutination is a valuable criterion for the simultaneous occurrence of immunizing processes.

This connection between agglutination and immunity has by no means been given up, but as the agglutination value often gives no definite clue in an individual case, more attention has lately been paid to the study of bacteriotropic substances and those producing fixation of complement. The agglutinins are by no means identical with the immune bodies, least of all can the content of agglutinins in the serum be considered as an indication of the actual degree of immunity attained, but they indicate the presence of specific reactionary processes in the organism.

Christian and Rosenblat [6] have made a valuable contribution to the importance of agglutination and the curative power of bacillary emulsion in experimental tuberculosis of guinea-pigs in their researches on the antibodies of tuberculosis and immunity to the disease. They succeeded in proving exquisite healing processes with very considerable formation of connective tissue in guinea-pigs during treatment with bacillary emulsion, at the same time showing the inconclusiveness of Jürgen's unsuccessful experiments on animals and the deductions which he drew from them.

#### (c) Opsonins.

##### The Opsonic Theory of Wright;

Wright's [41] opsonic theory is a work of great interest, and essential for the proper understanding of the cellular processes attending the specific therapy of many



infectious diseases, above all of tuberculosis; a work, further, which has again brought Metchnikoff's phagocytic theory into recognition. Metchnikoff had already made the observation that many infecting agents when introduced into the normal body called forth little or no phagocytosis, while in artificially immunized animals the process made itself actively felt. Further investigation showed that during immunization, substances were formed in the serum which stimulated phagocytosis (Metchnikoff's *stimulins*). More recent work confirmed the enormous significance in the mechanism of immunity of the taking up of bacteria by the cells, and showed that this happens under the influence of a substance of the nature of an amboceptor, called by Wright *opsonin*. Wright now elaborated a method enabling the opsonic power of a serum to be determined by a numerical comparison of the phagocytosed bacteria under constant experimental conditions. The ratio of the opsonic content of the serum of a patient to that of a healthy individual Wright calls the *opsonic index*, and this gives an objective standard of the content of the blood in antibacterial substances and a guide for therapeutic measures.

#### its Deductions and Practical Application.

Wright constantly found a period of intoxication varying with the amount of vaccine administered, during which the antibacterial power of the blood was reduced. On this negative phase followed a positive one, with increase of the antibacterial power, lasting in the case of tuberculosis for about a month. On this account he holds frequent injections of tuberculin to be useless, increasing the negative but not the positive phase. The proportion of antibacterial substances in the blood is also not proportional to the quantity of tuberculin injected. Wright accordingly worked with minute quantities of tuberculin, commencing with a dose of 0.0001 c.mm. (mostly new tuberculin, less with old), under constant control of the opsonic index during the negative phase. If the length of this increases the dose is too large; if it decreases it is evidence of the correctness of the dose. Wright has employed his method extensively in localized tuberculosis, pulmonary excepted, and produced perfect healing in severe cases of lupus, deep tubercular ulcers of the skin, large glandular swellings in the neck, as well as in cases of tuberculosis of bone, joints, and urogenital system. In mixed infections he immunizes both against the tubercle bacilli and the other infecting agent present.

#### Larger Doses Necessary.

Wright's method of dosage agrees with the requirements of certain other tuberculin therapists (such as Nournay and Jessen) that only the smallest quantity of tuberculin should be used, even in the treatment of pulmonary tuberculosis. According to our interpretation of the theory of tuberculin action, and after



many years' practical experience, the use of larger doses of tuberculin, though very gradually and cautiously increased, cannot be dispensed with. Many reasons can be given for this standpoint. The correctness of our view is confirmed by the works of Turban and Baer [42] on the practical significance of the opsonic index.

**Clinical  
Observation more  
Important.**

They are of opinion that the observation of Wright's rule—to make the dosage dependent on the phase—restricts the physician too much to the use of the smallest doses, which, apart from the treatment of severe cases, have little effect, and more easily produce hypersusceptibility than the larger ones. At any rate, the results obtained by Turban with larger doses of tuberculin without opsonic control were better, in spite of the fact that Wright's rule must certainly often have been broken. Turban and Baer take up our standpoint that in tuberculin treatment clinical observation (temperature, weight, subjective and objective condition, &c.) is more important than the determination of the opsonic index, "the marked fluctuations of which make the physician over-anxious and the patient hypersusceptible."

**Limitations of the  
Value of the  
Opsonic Index.**

In our opinion the present extent of our knowledge of the complicated behaviour of the opsonic index in tuberculosis, and especially in the form of most practical importance—pulmonary—does not speak for the value and utility of Wright's method. It has also been pointed out, especially by Löhlein (on the basis of Metchnikoff's observation in guinea-pigs with regard to the behaviour of the leucocytes to anthrax bacilli), that pathogenic organisms after penetrating into the body often acquire a greatly increased power of resistance to phagocytosis; and Löwenstein has made the observation that tubercle bacilli present in the body offer an incomparably greater resistance to phagocytosis than do those in culture. All observers, however, including Wright himself, agree it is just in cases of phthisis that the fluctuation of the opsonic content is exceedingly large; so large, in fact, that short walks, even simple bodily exercises, give rise to great variations of the index by introducing toxins into the circulation. This considerably limits the value of the opsonic determination. In addition, there is a point of great importance, which on the basis of our own observations we must hold as crucial: the complicated and difficult technique of the method, with its sources of error both numerous and incalculable.

How much the estimation of the opsonic index depends on the subjective judgment is evident from a communication made by F. v. Müller at the Congress of Tuberculosis Specialists at Munich in 1908, reported as follows in English literature: the same serum was given to eleven laboratories for



examination, and in almost every laboratory a different opsonic index was found; some gave it as positive, some as negative, the variation being from 0.8 to 1.7.

### Its True Significance.

In this way the opsonic index loses its practical value for a large section of practitioners who can and must take part in the specific treatment of tuberculosis. Its place as a difficult clinical method is in special institutions with assistants working at it alone, thus losing its significance in the treatment of a widespread disease. These considerations do not detract from the scientific value of Wright's teaching nor the forward step thus taken; it is calculated to confirm and intensify the conception held to-day of the beneficial effect of tuberculin in general, and especially to justify and strengthen the modern principle of a carefully graduated tuberculin treatment. We are of the same opinion as Neufeld [43], and for the present value the appearance of opsonins during specific treatment with tuberculin only in the sense "that we conclude from their appearance, just as from that of agglutinins, that a specific reactive process is certainly taking place in the organism without, however, any certainty that the opsonins are the immunizing substances which immediately bring about the healing process, and without even admitting that the quantity of these is a direct expression of the degree of immunity attained."

Even Wright and his pupils have given up the constant control of the opsonic index in the treatment of chronic cases of tuberculosis.

### (d) Phagocytosis.

#### Importance of Phagocytosis; Metchnikoff.

Phagocytosis, in Metchnikoff's sense, has in any case a *rôle* in the mechanism of immunity in tuberculosis during specific treatment, and we hold it to be of greater practical importance than the complicated determination of the opsonic index, as well as much simpler to demonstrate. But its significance is not nearly sufficiently recognized and explained.

According to v. Baumgarten, phagocytosis has no bactericidal action on the bacteria, the destruction taking place in the serum. From his investigations he concludes that the phagocytes at most digest dead organisms, and that phagocytosis disappears altogether in the immunized organism.

Other investigators, however, state that its utility cannot be doubted, whether it eliminates the tubercle bacilli from the circulation and prevents their increase, or whether, according to



Bartel and Neumann, it brings about the transport of the bacilli into the lymphatic glands and the spleen, which are to be considered the real organs of protection and destruction.

**Löwenstein.** Detailed work on phagocytosis in pulmonary tuberculosis has chiefly been published by Löwenstein [44], who has noted intracellular grouping of the bacilli in the leucocytes of sputum, often with decreased intensity of staining and retrogressive metamorphosis in the more favourable cases, especially those undergoing treatment with tuberculin. An interesting addition is furnished by the investigations of Morland [45], who noticed the intracellular grouping in patients undergoing specific treatment exclusively and almost regularly in the positive phase.

#### **Phagocyte Staining.**

We have confirmed Löwenstein's observations, but the microscopic proof is difficult with the usual Ziehl-Neelson or Gabbet staining method on account of the danger of damage to the protoplasm of the leucocytes. The following precautions are, therefore, advisable: cover-glass preparations are made with a platinum loop from about ten different parts of the sputum, the film being very thin and care taken not to damage the leucocytes. To this end Pfeiffer's injunction not to rub the slips on each other must be observed. The sputum is examined as fresh as possible to avoid the appearance in the leucocytes of degenerative changes. The preparation is carefully dried and fixed and then stained with carbolfuchsin over the flame; bubbles must on no account be allowed to rise.

#### **Significance of Phagocytosis.**

Present research shows that the process of phagocytosis is an extraordinarily widespread one, and is regularly present when the infection takes a favourable turn for the organism (Kruse [46]). Views only differ as to whether, as Metchnikoff's holds, phagocytosis is the causal factor, or whether, as most of the German workers in immunity consider, phagocytosis only occurs when the fate of the infecting agent is already decided by other bactericidal forces. But even so, it must not be forgotten that "an extraordinarily important service might be rendered to the infected organism, as simultaneously with the elimination of the already weakened or killed bacteria, a detoxication of the bacterial bodies, or at least a considerably slackened absorption of toxin, may take place, which in itself might be of decisive importance in the course of the process of disease" (P. Th. Müller [47]).

### **(e) Bacteriotropins and Bacteriolysins.**

**Löwenstein.** Bacteriotropins in tuberculin treatment have been studied by Böhme and by Löwenstein. According to Böhme [48], the serum of tubercular



patients not treated with tuberculin and also that of normal individuals may contain tuberculotropins. In slight cases they are found only in a relatively small percentage, in severe cases in the majority of patients. After treatment with bacillary emulsion these antibodies were relatively increased in all the sera examined.

**Böhme.**

In confirmation of Böhme's results, Löwenstein [19] proved that in clinically favourable cases, even when treated with old tuberculin, no increase of these bodies occurs; they appear to be connected with the employment of bacillary emulsion.

Both authors agree, however, that there is no strict connection between the course of the disease and the content of bacteriotropins.

This is not so in the case of bacteriolysins. According to the experiments of R. Kraus and Hofer [49] (on the lines of the well-known researches of Pfeiffer) tubercle bacilli in the organism can be destroyed by bacteriolysis as well as by phagocytosis. The bacteriolytic bodies for tubercle bacilli are produced in increased quantities in the tubercular organism and their presence can be proved in the serum. This raised bacteriolytic power of tubercular patients helps to explain their immunity to re-infection. They command a greater supply of bacteriolysins compared with healthy individuals but less opsonins and bacteriotropins, as Wright has shown. Therefore in the healthy organism the chief rôle is played by phagocytosis, while in the tubercular bacteriolysis is predominant in spontaneous healing and in immunizing processes. We have no very definite knowledge of the bacteriolytic bodies, especially as the normal serum of man and animal has a certain bacteriolytic power. We know, however, that they are present in increased amount in tubercular serum.

Many clinical observations point to the fact that the bacteriolytic resources of the organism are increased by specific treatment. Certain forms of the so-called reaction-fever, increase of sputum, disintegration of the tubercle bacilli, &c., are connected with it. Also Wolff-Eisner's and Sahli's explanation of the tuberculin reaction can be brought into line with it.

### (f) Complement-fixing Antibodies.

**Bauer and  
Engel's Results  
in Children.**

The appearance of the complement-fixing antibodies already mentioned in the blood of specifically treated tubercular patients seems to be of considerable significance. What Christian and Rosenblat [6] demonstrated in tubercular guinea-



pigs, Engel and Bauer [50] have confirmed in tubercular sucklings and young children; with appropriate tuberculin treatment they were uniformly successful in demonstrating the existence of antibodies producing fixation of complement in the serum, not formed like the agglutinins in normal cells, but in the tubercular tissue. Moreover, Bauer and Engel succeeded in proving by quantitative tests that with the quantity of tuberculin injected a corresponding amount of these antibodies was formed in the blood, increasing to a maximum. It deserves special notice that a considerable quantity of antibodies was only formed when relatively high doses had been reached.

Bauer and Engel's results in the specific treatment of tuberculosis in children agree with those of Jochmann and Möller [51 and 52] in adults. They succeeded in general in producing antibodies in the serum of the patients treated, and this only when he approached the maximum dose. They are more reserved with regard to the conclusions to be drawn from the phenomenon. They saw patients clinically completely cured with increasing formation of antibodies; others did as well without them; others, again, grew worse and died with continual increase of antibodies. In spite of these conflicting results, they with Koch looked upon the occurrence of the phenomenon as the indication of the formation of certain protective forces, which, in the cases which turned out unfavourably, may have come too late or not in sufficient quantity.

These results seem to prove the inferior value of exclusively small doses of tuberculin as expressly demanded by Wright's opsonic theory and by several authors.

The increase of antibodies can possibly be used as a general guide to the further course of treatment, so that the method of complement fixation may eventually prove valuable for the control and direction of specific treatment—a prospect which, by means of the continued estimation of agglutinins and the opsonic index, has not yet been fulfilled. It would also be of practical importance, as the technique of fixation of complement is one which can be carried out without difficulty in every institution and hospital.



## II.—The Specific Diagnosis of Tuberculosis.

---

### A.—General Section.

FOR the specific diagnosis of tuberculosis the following tuberculin tests come into consideration: (1) The cutaneous, (2) the conjunctival, (3) the subcutaneous.

**Diagnosis  
by Tuberculin  
Reaction.**

All tuberculin tests have this in common, that they make a diagnosis possible by the appearance of tuberculin reactions. These are to be taken as reactions of hypersusceptibility and analogous to immunity reactions, both cellular and humoral. On the other hand they are distinguished from one another by the fact that in the case of the cutaneous and conjunctival tests where the tuberculin is introduced into the tissue spaces of the skin or the mucous membrane, the reaction remains localized at the point where the tuberculin has taken effect; whereas subcutaneous injection brings the tuberculin into the circulation, and, in addition to general signs of reaction, sets free processes tending to hyperæmia and exudation in the tubercular focus.

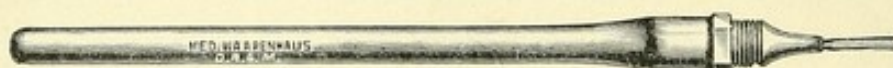
With regard to the specific nature of the tuberculin reactions it remains to be noted that they cannot appear quite regularly and equally clearly in each and every patient. And this on account of the dependence of every kind of biological reaction on the susceptibility of the organism, on its powers of reaction and reactionary products, and on the irritant power of the antigen in question. The conditions for tuberculin reactions are rendered specially difficult and complicated because almost every human being at some time or other harbours tubercle bacilli. But tubercular infection and tubercular disease are by no means identical, and only the latter interests the diagnostician. We must therefore be prepared for small but very essential deviations in individual tuberculin reactions.



## 1.—THE CUTANEOUS TUBERCULIN TESTS.

### (a) Cutaneous Test according to v. Pirquet.

**Technique.** The technique of the cutaneous tuberculin inoculation is very simple, and in general follows that of vaccination; it should, nevertheless, to exclude failure, accurately follow the directions of v. Pirquet. For implement a platino-iridium lancet will serve, or better, the specially constructed scarifier of v. Pirquet.



**Preparation Used.** The tuberculin preparation used is Koch's old tuberculin, and this may be conveniently stored in a bottle with ground-in pipette stopper, also suggested by v. Pirquet.

We have lately made an extensive series of experiments with Koch's tuberculin free from albumose side by side with old tuberculin, but cannot recommend the former, because when used cutaneously it offers no advantages from the point of view of diagnosis, is rather less reliable, and, moreover, is considerably dearer.

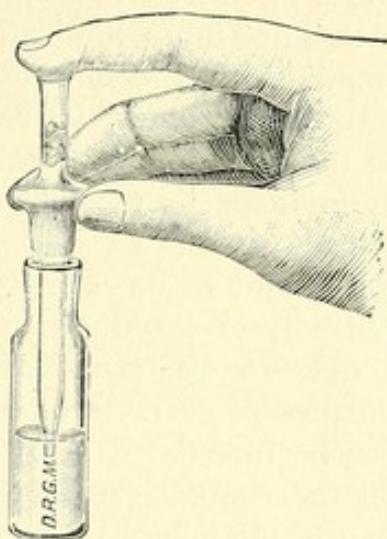
At first v. Pirquet [53] employed a 25 per cent. dilution with  $\frac{1}{2}$  per cent. carbolic acid, but quite recently has given the preference to undiluted tuberculin. If the latter is used the test need only be employed a single time, whereas a negative reaction with the 25 per cent. dilution renders the repetition with undiluted tuberculin advisable. The test is therefore simplified by the immediate use of the stronger preparation, but there is some justification for the objection that the reaction, which is already very delicate, becomes thus still more so, and is, in fact, too easily provoked. We have some observations of our own in which the cutaneous inoculation with undiluted tuberculin gave well-marked positive result in cases of clinically doubtful diagnosis, whilst the simultaneous test with 25 per cent. dilution as well as the fourfold repetition of the conjunctival test were negative, and this was finally confirmed by a negative result with the subcutaneous method.

On the other hand we have also noticed cases in which the first cutaneous inoculation with undiluted tuberculin was negative and only the second positive.

We recommend for adults the use of the undiluted tuberculin, and leave undecided whether for children the 25 per cent. dilution or the undiluted preparation deserves the preference.



For purposes of comparison one scarification can be treated with one and one with the other. In doubtful cases, in which the result is negative with 25 per cent., and positive with undiluted tuberculin, the subcutaneous method must decide.



The best site for inoculation is the inner side of the forearm, because of its delicate and less hairy skin and the ease of observation.

The skin is rubbed with ether, two drops of tuberculin



placed on it at a distance of about 4 in. apart, and circular scarifications made with the needle, first midway between the two drops and then in the middle of each.

It is sufficient to open only the most superficial lymph



channels by scraping off the layers of epidermis; any considerable oozing of blood is as much to be avoided as in vaccination. The process is made bloodless by seizing the forearm with the left hand, stretching the skin and making with the needle, held vertically between the fingers of the right hand, a rotatory scratching movement. The more delicate the skin the less pressure should be made with the chisel-like platinum end of the instrument. On the other hand, it is, of course, necessary to make a lesion; and the inoculation must be held to have been too superficial when, on inspection later, no kind of scab is to be seen.

The platinum point must be sterilized before use each time by heating it red-hot, to avoid the possibility of carrying over infections from case to case; and after every inoculation it must be carefully cleaned of every trace of adherent tuberculin, which might otherwise be inoculated into the control site of the next patient and spoil the comparison of the control inoculation with the others; or two needles may be kept, one for the control site, the other for the scarifications in the drops of tuberculin.

After the inoculation the tuberculin is allowed to soak into the tissue spaces for some minutes, or a piece of cotton-wool is applied, small enough to be quite soaked by the drop. No dressing is necessary.

#### Inspection of Result.

The most favourable time for a single revision of the inoculation is after a period of forty-eight hours. If daily inspection is possible the result should be controlled after twenty-four and forty-eight hours, and in order not to overlook the possible occurrence of a late reaction, again after three, four, and eight days.

In interpreting the reaction a distinction must be made between :—

- (1) The traumatic reaction arising from the scarification itself.
- (2) The inoculation with negative reaction.
- (3) The positive cutaneous reaction.

As this is in practice not always quite easy and may lead to errors of diagnosis, the differences between them will now be discussed in detail, based on 800 observations of our own in adults and on v. Pirquet's much larger clinical material in children.

**Types of Reaction ; the Traumatic.** The traumatic reaction arises within a few minutes at the site both of control and inoculation, and in the same way. It consists as a rule of a small raised area, in



the middle of which, later, a scab, the size of a pin's head, appears where the epidermis has been damaged. A slight redness in the immediate neighbourhood of the scarification is usually still visible after twenty-four hours, and then disappears, leaving only a small brown scab on the natural skin during the next few days. After the scab has fallen off a fine pale scar is visible. The intensity of the traumatic reaction is dependent on the depth of the scarification and on the individual reactivity of the skin (*vide* control sites on Plate I).

#### **The Negative Reaction.**

The inoculations with negative reaction give rise to the same appearance as the control site lying between them: they appear in the first twenty-four hours slightly swollen. The distinction from minimal specific reaction demands a certain amount of practice. Hence v. Pirquet recommends the beginner to regard reactions under 5 mm. in diameter as doubtful, and in such cases to repeat the inoculation, as a positive reaction becomes more marked on repetition.

We can only concur in this now that Ellermann and Erlandsen have proved that the positive result of the second cutaneous inoculation after a previous negative reaction is to be attributed to a universal sensitization of the organism, but that tuberculin is not capable of sensitizing an organism perfectly free from tuberculosis.

#### **The Positive Reaction.**

The positive cutaneous tuberculin reaction has a latent period varying from three hours to several days; in most cases it is well developed after twenty-four hours, and most distinct after forty-eight. The inflammatory reaction caused by the specific action of the tuberculin consists in hyperæmia and exudation, and appears as a slightly raised reddening, starting from the roughened spot of skin, and increasing rapidly in extent and height. An inoculation papule arises of individually very various extent and intensity; on the average the diameter measures about 10 mm., occasionally 20 mm., and only in exceptional cases, with very severe reaction, does it extend to 30 mm. The edge of the papule is circular or irregular, or it may be rendered indistinct by small follicular swellings on the margin; in intense reactions it is surrounded by a flat, slightly bluish-red areola (vaccinal area).

Plate I shows the appearances of a slight and of a well-marked cutaneous reaction.

The maximum of the reactive signs is generally reached forty-eight hours after the inoculation; then the exudation



decreases, the redness fades, passes over into violet, and gradually into a pigmentation which may remain visible for weeks. Then follows a slight peeling of the epidermis.

From this fundamental type of cutaneous reaction there are numerous variations in respect of latent period, development and disappearance.

Thus a reaction beginning after from six to twelve hours, generally very weak and ceasing after twenty-four hours, is described as a rapid reaction; it is so very rare that it is of no practical importance. More frequently a prolonged reaction is observed, which occurs after from six to fifteen hours, and remains as a very marked papule more than four days, sometimes for weeks and months.

#### Aberrant Types of Reaction.

If the latent period exceeds twenty-four hours it is a *late* reaction, which, according to v. Pirquet, occurs principally in cases clinically unsuspected, and only exceptionally (*torpid* reaction) in manifest tuberculosis.

In respect of colour the papules show the most various grades; in general they are bright red in well-nourished subjects with healthy skin colour, pale red in anæmic patients, and colourless (without hyperæmia) or livid (without exudation) in the last stage of fatal forms of tuberculosis. In those cases in which the papule is only recognizable by the sense of touch or by lateral illumination, v. Pirquet speaks of a *cachectic* reaction.

Finally the *scrofulous* reaction deserves special mention, a reaction observed by v. Pirquet chiefly in scrofulous children and with its small warty nodules in the immediate neighbourhood of the papule proper, reminiscent of the appearance of lichen scrofulosorum. Of such reaction we have seen isolated examples in phthisical adults.

If the cutaneous inoculation is doubtful or negative, and is then repeated after some days, a positive reaction frequently appears; now and then also a late reaction at the previous site of inoculation. This so-called *secondary* reaction manifests itself in v. Pirquet's experience with children principally when the tubercle cannot clinically be demonstrated, corresponding to the torpid or primary late reaction already mentioned.

The specific nature of the cutaneous tuberculin reaction, occurring as it does only in the organism infected with tuberculosis, is practically confirmed by observations at the bedside and *post mortem*. Specially conclusive in this respect are the experiences of v. Pirquet [53] and Ganghofner [54] with a large number of



children, the indications given by the cutaneous test being confirmed by *post-mortem* examination. Sörgo's objection that the cutaneous reaction to tuberculin—just as to other toxins, *e.g.*, of diphtheria, dysentery and cholera—is to be ascribed to a common non-specific cause—an increased sensitiveness of the skin of tubercular individuals—has been refuted by Zieler's [55] accurate experiments.

The structure, too, of the papule points to its origin in a histological reaction of a specific kind. Daels [56] cut serial sections of the papules of the late reaction and found "elongated nodules with central giant cells of typical Langhans form, and with epithelioid and round cells at the periphery," changes identical with the specific structure of tubercular tissue or of the tubercle itself.

Zieler [55] saw far beyond the sites of inoculation tubercles with typical Langhans giant cells in their blood-vessels deep into the subcutaneous tissue.

The tubercular modifications at the sites of inoculation, which are proved by histology, suggest the idea of contra-indications of the cutaneous reaction. On this point very little has been written, and this shows that only where there is an exceptionally high degree of hypersusceptibility to tuberculin can existing scrofulous changes appear more clearly or for the first time in other parts of the body (distant reaction).

#### Possible Mischief from Reaction.

As a sequel to the cutaneous tuberculin test scrofulous changes (phlyctenules, generalized lichen scrofulosorum) were noticed in tuberculin children, the formation at the site of inoculation of a chronic ulcer the size of a pea in an adult with scrofuloderma, also changes in the skin similar to scrofuloderma and phlyctenular conjunctivitis in scrofulous children.

It has further been established that the cutaneous inoculation has a certain influence on the body at large; but this only, as a rule, makes itself felt as fever, local reaction, and affection of the general tuberculin susceptibility when, in performing the inoculation, incisions have been made and the tuberculin has through these reached the deeper layers of the skin and thence the circulation. The rise of temperature, which in these cases begins with the development of the papule, is, however, never high (about 2° F.) nor of long duration. When the platinum scarifier is used we have never observed fever or other symptom of general reaction.

The harmful results of the cutaneous test enumerated above are numerically—in comparison with the enormous number of



reactions carried out—so infinitely rare and in themselves so insignificant that they hardly deserve the name. In fact the cutaneous tuberculin reaction, carried out *lege artis* according to v. Pirquet's directions, is a diagnostic method as harmless as it is easy, which, thanks to its simplicity and freedom from risk, is suitable for use in the earliest childhood, and to which in respect of practical application no contra-indication can be raised.

#### Assent of the Patient.

The question, however, whether it is necessary before making use of the cutaneous test to obtain the permission of the patient, or in the case of children the permission of the parents, is answered by Bumm [57] in the affirmative from the legal point of view. Even from the point of view of expediency, however, the physician will do well only to inoculate when a patient or his legal representative has actively or passively given his assent. It is allowable for the physician to obtain his consent through a third person (a teacher, for instance), or it may be included in the general acceptance of the conditions of admission to the hospital.

#### Indications.

The indications are given by the course of the reaction and its effects. The following points must be considered in connection with these:—

The specific nature of the intracutaneous test cannot be disputed for the same reasons as apply to the specificity of the cutaneous and percutaneous reactions.

The specific inflammatory symptoms of the cutaneous inoculation occur without accompanying rise of temperature or other symptoms of a general reaction; they indicate the presence of tuberculosis in an anatomical sense.

#### Positive Result.

The positive cutaneous reaction gives no information as to the site of the disease, or its activity or inactivity. It only shows that the body somewhere and at some time has been infected with tubercle bacilli. Therefore not only those manifestly tubercular react but also those who are clinically non-tubercular. That is specially important in the diagnosis of adults, in whom the positive cutaneous reaction alone does not afford any practical conclusions as regards treatment. With adults the cutaneous reaction is only of importance when considered in conjunction with the clinical appearance of the disease. When it is very distinctly positive, accompanied by considerable infiltration or extensive reddening in the vicinity of the inoculation site and only slowly disappears, then very thorough examination and observation of the patient is imperative.



**Negative  
Result:**

The negative result of the test speaks in general for the absence of tuberculosis. But the reaction may fail in spite of the presence of actual tuberculosis capable of clinical demonstration. This is then to be explained by the nature of the tubercular process (fungoid, fistulous, or suppurating), by the local or constitutional condition of the inoculated subject (condition of the skin, general cachexia), by tuberculin immunity after specific treatment, or by other circumstances, *e.g.*, during measles, the incubation stage of scarlet fever, the continuance of high intermittent fever, and in pregnancy.

**In Measles and  
in Pregnancy,**

According to v. Pirquet the absence of any cutaneous reaction during measles, as well as in miliary tuberculosis, is caused by the absorption of the ergins (the bodies which bring about the clinical reaction between the tuberculin and the cells). "Considered in this light the decrease in the tubercular allergia during measles is brought into harmony with the fact that in connection with the disease there so often occurs a dissemination of tuberculosis." In the same way Stern explains the decrease in activity of the cutaneous reaction during pregnancy to the fixation of the antibodies to the lipoids of the placenta or of the blood. In the same way can be explained the unfavourable effect of pregnancy on patients suffering from tuberculosis.

**and in Pneumonia,  
Diphtheria, &c.**

Rolly [58] has also at various times systematically tested the powers of reaction to tuberculin of the skin of patients suffering from croupous pneumonia, enteric fever, diphtheria, erysipelas, polyarthritis rheumatica, and angina follicularis. He discovered that in the majority of cases during the course of these diseases a negative condition persists, while a distinctly positive reaction is obtained during convalescence. He considers the reason of this change in the same individual to lie in general not in special immunizing processes, but more probably locally in a changed condition of the skin. We are of the same opinion, and also agree with Rolly that the skin may, under various conditions, be very slightly or not at all allergic, but that the organism, on the contrary, may at the same time be very susceptible to tuberculin.

**Non-appearance of  
Reaction in  
Moribund Cases.**

The cutaneous reaction regularly falls in the last days of a fatal case of tuberculosis, when the reacting power of the patient has become non-existent either by becoming accustomed to the tubercular virus, or in consequence of cachexia. It often fails in cases with hæmatogenous extension of the process,



in miliary tuberculosis and tubercular meningitis; in severe cases of the last two, repeated inoculations of the same patient may even give varying results. The cutaneous reaction seldom fails where tuberculosis occurs along with some other disease; in this case the late reaction acquires a certain importance in the diagnosis whether it appears late after the first inoculation or only becomes positive on a repetition of the test.

The knowledge of the non-appearance of the positive cutaneous reaction in spite of the presence of tuberculosis leads us in such cases to abandon cutaneous inoculation altogether from the very first, or at least to be very cautious in our estimate of the result.

**Diagnostic Certainty of the Reaction.** Apart from these exceptions and the failure to differentiate between active and inactive tubercular processes, the diagnostic certainty of the cutaneous reaction is in other respects great. From our own experience the cutaneous reaction with undiluted tuberculin was positive in 96 to 98 per cent. of adult tubercular patients [59]. This percentage decreases in cases in the third stadium of the disease. Other statistics show similar results, especially those of v. Pirquet for children: 97 per cent. of the positive reactions showed undoubted naked-eye appearances of tuberculosis at the autopsy, whereas all the children who were found on the *post-mortem* table to be free from tubercle had given a negative reaction.

**Prognosis.** From the prognostic point of view, cutaneous inoculation is of little value, and only to be considered in conjunction with the results of the clinical examination, any possible complications, hygienic conditions and other external circumstances. Considered by itself, neither a positive nor a negative cutaneous tuberculin reaction justifies prognostic conclusions. On the other hand the repeated failure to obtain a cutaneous reaction in obvious tuberculosis generally points to a bad prognosis and that often at an earlier period than the clinical examination. And a well-marked positive cutaneous reaction can be looked upon as an almost certain "indication of the power to fight against the tubercle bacillus." That is to say, when it is attained with diluted tuberculin it aids in making a relatively favourable prognosis of the course of a case of manifest tuberculosis. Whether repeated graduated inoculations at long intervals have any prognostic significance is still doubtful. It is probable that an increased and more rapid cutaneous reaction is general in favourable clinical improvement of active tubercular processes, just as high cutaneous reactivity of patients not undergoing



specific treatment usually goes hand in hand with favourable general condition and large content of antibodies. On the other hand, the graphic record of the course of the reaction—normal, rapid, prolonged reaction—is of no assistance in prognosis, not even to distinguish active from inactive tuberculosis.

#### Quantitative Test.

In order to distinguish active processes of tuberculosis from inactive, Ellermann and Erlandsen [61] have experimented with the quantitative method of cutaneous inoculation, using graduated concentrations of tuberculin.

For these very finely graduated inoculations they chose concentrations of a standard tuberculin of 0.1 per cent. rising to 50 per cent. and noted the dilution which produced absolutely no cutaneous reaction. The reciprocal value of this tuberculin dilution is then a measure of the power of reaction, the "tuberculin titre of the organism."

According to the experiments of Erlandsen and Petersen [60], the tuberculin titre should be 0 in persons free from tuberculosis, it should remain below 100 when the tuberculosis is inactive, and rise to 200-400 when active tuberculosis is present. It should go back to below 100 when the tuberculosis has become inactive and drop sharply a short time before death. Only in cases of tuberculosis of the glands and bone would there be generally a high tuberculin titre for a very long time. Although one cannot diagnose tuberculosis from such estimations alone, yet, in conjunction with other clinical aids, a high tuberculin titre supports the diagnosis of active, and a low titre the diagnosis of inactive, processes of tuberculosis.

Erlandsen [61] has lately drawn up a table for calculating the tuberculin titre. The breadth in millimetres of a papule corresponding to a 4 per cent. tuberculin solution ( $p_4$ ) and the difference in the breadth of this papule in millimetres after twenty-four and forty-eight hours ( $d_4$ ) are determined. The tuberculin titre can then be read off from the table.

Lossen, S. Möller, Mirauer, Wallerstein, Waltershöfer, and others have come to the conclusion from their own experiments that graduated tuberculin concentrations are of no practical use in distinguishing active and inactive tuberculosis.

We also, from our own experience with quantitative cutaneous tuberculin tests, must reserve our opinion and cannot recommend them in practice. The idea that the cutaneous reaction can only be useful in the case of adults when graduated doses of tuberculin are used may be excellent, but the method of applying it is open to too many inexactitudes and inaccuracies to be reliable. Moreover, we are dealing with conditions of great hypersusceptibility which are characterized by too great individual variations and do not give reliable information for the diagnosis of the nature of the tuberculosis.

For this reason we do not consider the method recommended by Ditthorn and Schultz [62] of cutaneous inoculations with iron tuberculin (iron precipitates of tubercle bacillary substance)



to be promising in the differentiation of active and inactive tuberculosis. Schellenberg [63] confirms this on the ground of detailed experiments; the strong positive iron-tuberculin reaction is not a guide to activity or inactivity of the disease; and the assertion that iron tuberculin does not call forth a reaction in latent or inactive tuberculosis is incorrect.

**General Verdict** The general verdict as to v. Pirquet's  
**on** cutaneous reaction may be expressed in  
**Cutaneous Test.** the most general form conceivable: Its application may be extended to all the circumstances of general and hospital practice, for it is extremely simple for the physician and can be used at any time in consultation hours, and also in the case of feverish patients and those in bed. It is a perfectly harmless action, involving no danger and, carried out *lege artis* according to v. Pirquet's direction, works without causing any malaise, fever, local or general disturbance or complications of any kind.

The real scientific and practical importance of the cutaneous tuberculin test is certainly limited to early childhood, to the first two or three years of life. Here it triumphantly proves itself to be a great and genuine discovery. It may also be successfully used in the investigation of tuberculosis in children of school age and leads to suitable hygienic prophylactic measures for the protection of the rising generation at home, in public, at school, &c. It is a diagnostic medium *par excellence* in children's practice, to which we will return later in a special chapter. But it is also true here that only the clinical condition in conjunction with the cutaneous reaction must decide as to the treatment of the individual case.

In veterinary practice the cutaneous test is of no practical importance.

**Detre's** In order to differentiate cases of tuber-  
**Differentiations of** culosis Detre [64] modified v. Pirquet's  
**Cases by a** method by using three different kinds of  
**Modified Test.** tuberculin for the cutaneous inoculation: (1) Koch's old tuberculin; (2) the filtrate from a culture of human tubercle bacilli; (3) the filtrate of a bovine culture. According to the appearance of the individual papules he then divides the cases into those susceptible to human and those susceptible to bovine bacilli. In this way Detre thinks it possible to come to a decision as to the nature of the infecting virus, and that the organism will react most powerfully to the toxin of that type of bacilli which has infected it. According to the results obtained by Detre, pulmonary tuberculosis, for



instance, showed a preponderating reaction (more than 90 per cent.) to human bacilli, but visceral and surgical tuberculosis to bovine (30 to 50 per cent.), so that it appears to him that the human type of tubercle bacillus is specially suited for pulmonary tuberculosis and the bovine bacillus for tuberculosis of the bones and glands.

v. Gebhardt also saw a preponderating reaction of the bovine type in surgical tuberculosis and of the human type in internal tuberculosis. On the other hand, according to Schroder, patients suffering from pulmonary tuberculosis always react cutaneously at the same time to bovine and human tuberculin, to the latter generally more severely. Similar observations in adult tuberculosis were made by Friedrich, Laszlo, Raw, the authors, and others. In consideration of these results and the now undisputed fact that human pulmonary tuberculosis is, with very few exceptions, to be ascribed to an infection with tubercle bacilli of the *typus humanus*, we cannot accept Detre's statement that about every tenth case is etiologically of bovine origin.

But this does not affect the observation made by Monti, Heim, John, v. Gebhardt and others, that cases of internal and surgical tuberculosis, especially in children, react cutaneously in varying degree both to tuberculin in general, and also to various kinds of tuberculin. This is because the surgical tuberculosis of greater cutaneous reactivity offers greater resistance and defence against the tubercle bacillus and is therefore more favourable as regards prognosis than internal tuberculosis. The difference of time in growth on culture-media of human and bovine bacilli may also cause differences in the reaction; on this fact depends the observation first made by Carl Spengler, that bovine toxins are far less toxic for tubercular patients than the human. Thus it is only a question of quantitative differences in a group reaction which as such do not permit of differential diagnostic conclusions. Lastly, differences may be caused by the scarifications being of unequal depth, by the effect of the tuberculin in question not always lasting the same length of time, by the conditions of absorption not being the same, and so on. On the whole, we do not hope for much practical success from a differential cutaneous test.

### **(b) Percutaneous Tuberculin Test of Moro.**

The absorption of tuberculin through the skin, introduced by Carl Spengler for therapeutic purposes, has been also utilized for diagnosis by Moro and Doganoff [65].



Moro [66] recommends the inunction of a tuberculin ointment consisting of equal quantities of Koch's old tuberculin and anhydrous lanolin.

B Tuberculini Kochi      ...      ...      ...      5'0 gramm.  
 Lanolini anhydrici      ...      ...      ...      5'0 „  
 M. fiat ung.  
 Sig.—Tuberculin ointment for physician's own use.

In the preparation of the ointment care must be taken that the lanolin, which of all vehicles allows of the greatest concentration of the ointment, should be heated to 20° to 30°. The ointment, which when fresh is of a pale yellow colour, becomes somewhat darker after a time, but if stored in a refrigerator remains potent for months. For each inunction a piece the size of a pea only is used, so that 10 gramm. of the ointment suffice for some 100 tests.

For practical purposes it is advisable to obtain the ointment in small tubes containing 2 gr. Moro's attempt to apply tuberculin plaster to the skin has not proved successful in practice, as the necessary concentration of tuberculin deprived the plaster of its adhesiveness.

#### Method.

As site for inunction, Moro recommends the abdominal wall beneath the ensiform cartilage, or the skin of the chest in the neighbourhood of the nipple, and states emphatically that the skin of the fore-arm is unsuitable. Inunction is carried out with moderate pressure of the finger; a protective rubber finger-stall is not necessary, for a reaction never takes place on the palmar surface of the finger used for inunction purposes. The duration of the inunction is half to one minute, the diameter of the area about 5 cm. After the inunction the part should be left exposed for a few seconds; no dressing is necessary.

#### Types of Reaction.

The positive percutaneous reaction appears in different grades analogous to the cutaneous reaction. We see in adults and children, as slightest grade, single or numerous, isolated, more or less distinct, reddened spots, which are only visible on the most careful inspection and disappear in a few days—miliary reaction (see Slight Percutaneous Reaction, Plate I). We observe as well-marked reactions papules indistinguishable in degree of hyperæmia and exudation from those of the cutaneous inoculation—confluent reaction. And we see, on an inflamed base, red nodules arise, which sometimes have at the head a vesicle filled with turbid matter—vesicular reaction (see Well-marked Percutaneous Reaction, Plate I). Intermediate to these



are combinations of the individual reactions. The more severe reactions, which are not always limited to the site of the inunction (disseminated distant reaction), are generally accompanied by itching and last several days, then gradually fading with slight peeling and pigmentation of the skin.

The percutaneous reaction generally takes place after twenty-four to forty-eight hours, but as it also sometimes appears after three to four days, the patients must remain under observation more than two days.

**Specific Nature.** Of the specific nature of the percutaneous reaction there is as little doubt as of the cutaneous.

This is not in any way affected by the observations made by Moro, Kanitz, and other writers, that in purpura, epilepsy, chorea, and herpes zoster, the percutaneous as well as the cutaneous test frequently gave, even in clinically unsuspecting cases, positive results. All these cases have, at some time or other in their lives, got the better of a tubercular infection, and the positive reactions signify no more than that those illnesses often attack individuals infected with tuberculosis.

The indications for the percutaneous tuberculin test depend upon the question—whether it is harmless and free from danger and whether its results are sufficiently reliable to be valuable for the purposes of diagnosis. The literature now existing on this subject is sufficient to clear the matter up.

**Diagnostic  
Value.**

Moro tested the percutaneous skin reaction on the large number of child-patients in the Munich University Children's Hospital and Polyclinic, with the result that of the manifestly tubercular children 17 per cent. did not react; these were principally children with miliary tuberculosis and meningitis, whilst all cases with negative percutaneous reaction were seen in the *post-mortem* rooms to be macroscopically free from tuberculosis. Comparative investigations of the percutaneous and cutaneous tests revealed a striking parallelism, not only in the general results of the tests, but also in all the minute details of the reactions. The inunction test is on the whole somewhat less sensitive both in manifest cases of tuberculosis and in cases not clinically suspect. This is, however, of no real advantage, because the limitation is small in childhood, and ceases after the age of from 10 to 12.

In cases of surgical tuberculosis Moro observed almost always a strikingly intense reaction, whilst these were not usual in cases of pronounced scrofula. In the first six months of life the percutaneous reaction was so frequently negative in spite of existing tuberculosis, that also at this period of life it cannot be made use of with any certainty in opposition to the clinical diagnosis.



**Disadvantages.** The disadvantages of the percutaneous test lie in the fact that the more severe reactions set up rather violent irritation and, especially in scrofulous children, show a tendency to spread also to other parts of the body. Disseminated, grouped or girdle-shaped reactions in distant parts of the skin, lichen scrofulosorum, also general exanthema have been observed.

According to the observations of Emmerich, Wetzell, Heinemann, Bullinger and others, the inunction reaction is of more value clinically for children than for adults, in whom it also indicates inactive foci.

Adult tubercular patients with atrophic skin may give a negative reaction to the first inunction and a positive to the second if greater pressure is applied, lasting more than one minute. Control inunctions with ung. ciner., soft soap ointment, chrysarobin, lenigallol and other ointments have given quite negative results, except in patients with very delicate skin and exceptionally strong dermatography.

We have employed the three tests (cutaneous, conjunctival, and percutaneous) simultaneously on 100 cases of definite cases of adult tuberculosis in all stages, and have obtained the most varied results. Sometimes all three reactions were positive, sometimes two, sometimes only one. The percutaneous test on the inner side of the fore-arm, after rubbing the skin with ether, gave the fewest positive reactions.

From this it is clear that the percutaneous test is decidedly inferior to the cutaneous in point of definiteness. This seems readily intelligible when we consider that the condition of the skin—thickness of the epidermis, number and size of the pores, amount of moisture, excitability of the nervous system—must have an essential bearing on the result of the test. Where the skin is thick, dry, scaly or atrophic, the inunction test is useless, even when the other conditions for the occurrence of the reaction are present. Moreover, the duration and intensity of the friction play an important part. All these external influences must have much more influence here than in the cutaneous test, where the possibility of the undiluted tuberculin acting is, to a certain degree, guaranteed by the injury to the skin. It also follows from this that the percutaneous test cannot be preferred to the cutaneous for indicating activity in the tubercular foci.

**Conclusions.** There are no contra-indications to the percutaneous tuberculin test, except in the case of pronouncedly scrofulous children, when there is a danger of distant reactions or general exanthema.

From the positive result of the inunction the presence of a tubercular focus, though it may be without any importance



whatsoever, may be concluded, without information as to the locality, the active or inactive character of the infection.

If the reaction be negative, this does not in any way prove the absence of tuberculosis. It almost regularly fails in early infancy, in cases with hæmatogenous diffusion of the process (meningitis, miliary tuberculosis) and during measles, sometimes also in cachectic patients, even when the presence of tuberculosis has been clinically clearly demonstrated. This happens so frequently in the case of definitely tubercular adults that express warning must be given against attaching any value to negative results of the inunction test in diagnosis in the case of adults.

The value of the percutaneous tuberculin test in diagnosis is therefore much greater in children, except during the first six months of life, than in adults. A positive reaction in children points with much more probability to the presence of active tuberculosis.

It can therefore be employed instead of the cutaneous reaction when the latter is not allowed from fear of "inoculation." It is also to be recommended when the physician does not wish to declare his suspicion of tuberculosis to the child's parents. In this case, a small portion of the child's skin can easily be rubbed with the ointment on some pretext or other.

The tuberculin inunction test has no value in prognosis.

The methods recommended by Lignières and Lautier are merely modifications of Moro's inunction test.

**Lignières' Modification.** Lignières [67] rubs into the well-shaven skin five to six large drops of undiluted tuberculin for one to two minutes. Within one or two days, if the patients are tubercular, there arise isolated or partly or entirely confluent papules, in children sometimes in two or more sets.

Lignières' modification does not seem to us to possess any advantages. It has, on the other hand, a disadvantage not to be made light of. There exists the possibility that the use of the razor may produce superficial lesions of the epidermis, and therewith the danger that an altogether uncontrollable quantity of the "five or six large drops of undiluted tuberculin" may be absorbed and produce a general reaction. We, therefore, reject it as superfluous and harmful.

**Lautier's Modification.** Lautier [68] places a swab of cotton-wadding, soaked with two or three drops of 1 per cent. tuberculin, on the outer surface of the arm without any previous preparation of the skin,



and fastens it on with a bandage. After twenty-four to forty-eight hours this produces in tubercular patients an inflammatory redness. We consider this modification also to be unreliable.

### (c) Intracutaneous Tuberculin Test.

Mendel [69] noted in tubercular patients after intracutaneous injection of quite small quantities of tuberculin a characteristic local reaction due to hypersusceptibility, but he could not study it further for want of clinical material. This was done later by Moussu, Mantoux and Roux, who recommended the "Intra-dermal Reaction" for the diagnosis of tuberculosis.

Independently of these French authors, van Balen and later Möller have used the method, employing varying concentrations to obtain information as to the reactivity of tubercular affections.

#### Method.

According to Mantoux and Roux [70], the intracutaneous tuberculin test is carried out as follows: One drop of a dilution of old tuberculin, 1:5,000 (= 0.01 c.mm.) is injected into the whole thickness of the skin. After taking up a fold of the skin of the anterior surface of the thigh, the fine sterile needle of a Pravaz syringe is inserted almost parallel to the surface, care being taken that the point of the needle after the puncture is directed rather upwards (epidermis) than downwards (hypodermis). The injection has been successful if it is immediately followed by the formation of an œdematous nodule of about 4 mm. in diameter, which disappears after a few minutes.

The solution required for the intracutaneous test as suggested by Mantoux and Roux is prepared by mixing 1 c.c. of 1 per cent. tuberculin with 49 c.c. normal saline immediately before the injection. A *single* drop of this solution must be injected *into* the cutis.

We will not describe the technique of the intracutaneous test as specially difficult; however, it does not seem altogether an easy matter to allow exactly one drop to fall from the needle lying in the tissues and to perform the test entirely intracutaneously. For when the injection is made in the subcutaneous tissue, febrile symptoms may occur.

**Engel's Method.** The method suggested by Engel [71] is simpler, less painful, and practicable even with restless children: the puncture is made with a very fine, short needle, flat in the skin on the back of the fore-arm and by pressure on the piston of the syringe—a small wheal about the size of a lentil is produced. The white wheal disappears in about



a quarter of an hour, and except for the puncture hole there remains nothing to be seen until the intracutaneous reaction takes place (Plate I). Engel makes the test in the first place with a tuberculin dilution of 1:5,000 and repeat it if the result is negative. He raises the concentration to 1:1,000, then to 1:100 and finally to 1:10.

**Positive Result.** A positive reaction takes place in five to six hours in the form of infiltration, perceptible to touch or sight. After twenty-four hours the infiltration is increased, reddish, sometimes oedematous, with an erythema-like edge. It reaches its highest point in the course of forty-eight hours. The extent and intensity of the reaction vary in different individuals. In some small red papules are formed, while in others their diameter measures 15 or 20 mm. Also pronounced infiltration extending over a surface as large as the palm of the hand, with inflammatory reddening and swelling of the surrounding tissue and blister formation in the centre, sometimes occurs (Plate II).

In another two days the reaction gradually diminishes, sometimes with scaling of the skin; it is, however, generally visible for several weeks. Mantoux states that in a positive reaction there are "hardly any general symptoms"; very slight fever may occasionally be noted. Engel describes the unpleasantness for the patient by his method as "minimal," especially as febrile symptoms never occur. After our experiences with adults we cannot agree; even slight reactions cause discomfort lasting for days, at any rate irritation and itching. The more severe reactions considerably limit the utility of the arm, pain in the arm and axilla not seldom being present; we have also repeatedly found glandular swellings as a sign of a tubercular focal reaction.

**Negative Results.** If the test is negative, there appears only a small induration with slight telangiectasis or slight blue-brown coloration, phenomena which have quite disappeared in two or three days. As a positive reaction would by this time have reached its height, mistakes in the judgment of the intracutaneous test are practically excluded.

**Mantoux.** According to Mantoux [72], the intracutaneous is the most definite of the local tuberculin tests. If the result is negative, tuberculosis may with certainty be assumed to be absent unless the patient is cachectic or suffering from measles in the incubatory stage. On the other hand a positive result proves the presence of tuberculosis in the body of the patient.



**Monti.** Monti [73], who has made the test on 374 children exactly according to Mantoux's directions, recommends it for general practice when the cutaneous test has given a negative result: the possible presence of latent tuberculosis will then be recognized.

**Engel.** Engel [71] considers the greatest advantage of the test to lie in the fact that by employment of varying strengths of tuberculin, even the highest concentrations, the reaction can be produced under all circumstances. Provided the necessary rise of concentration is observed, no case which gives a negative test can harbour tubercular foci. Therefore the intracutaneous reaction offers the security of discovering tuberculosis when the tuberculin susceptibility of the organism is reduced by acute infections, cachexia or hæmatogenous extension of the tubercular infection; it is of assistance where the cutaneous reaction has its natural limits. It is further applicable in febrile conditions and when miliary dissemination is suspected, thus in cases where the subcutaneous test is strongly contra-indicated.

**Indications.** The intracutaneous reaction is indicated when the cutaneous test is negative or gives no reliable result; also when there are objections to the subcutaneous test and when extreme certainty is necessary in excluding tubercular infection from the diagnosis.

Roemer and Joseph [74] also consider possible the quantitative estimation of hypersusceptibility in patients with tubercular infection by the intracutaneous method, and claim that the result of the test will show whether the case in point is one of tubercular infection only or tubercular disease. We cannot share this optimism based on animal experiment on account of our own observations in tubercular adults, and the same considerations which show Ellermann and Erlandsen's quantitative method to be unsuited for the purpose. Möller shares this view.

To give a general judgment of the intracutaneous test, its advantages must be weighed against its drawbacks. The latter are its greater technical difficulty and the discomfort and often pain in the area of reaction; the former chiefly lie in the fact that it is superior to the cutaneous method in its accuracy in indicating tuberculosis and is applicable to cases where the subcutaneous test is contra-indicated. Its sphere of utility seems to be limited to early childhood. In adults the intracutaneous reaction is no more conclusive than the cutaneous, thereby losing its value.

**Veterinary  
Application.**

In veterinary medicine the intracutaneous reaction has proved valuable. Although there is at present no prospect of the



method being chosen for the official tuberculin tests on cattle at frontier and quarantine stations, yet it has proved itself a valuable aid in animal experiments.

Roemer [75] recommends the following proceeding in veterinary practice: With cattle, shave at the side of the neck a square surface of about 10 cm., and inject into the skin with a syringe 0.1 c.c. of 50 per cent. tuberculin, the dilution being made with normal saline. If the reaction is positive, a considerable, often painful, swelling of the skin takes place, the extent of which may be exactly estimated after forty-eight hours with the help of calipers, and compared with the thickness of the skin ascertained in the same way before the injection. Differences in the thickness of the skin up to 0.4 cm. may be considered as negative, 0.5 up to 0.7 cm. as doubtful, and swellings of more than 0.7 cm. as distinctly positive reactions, provided that an injection of 50 c.mm. tuberculin in 0.1 c.c. fluid is given, and for measurement two points on the shaven surface of the skin exactly 5 cm. apart are chosen and compressed with the fingers for the adjustment of the measuring apparatus. In the results, Roemer found complete agreement between the intracutaneous and subcutaneous reaction, and also in pigs an absolute, and in cattle an almost invariable agreement between the result of the reaction and the condition of the animals as seen after slaughter.

The results obtained by Martin, R. Kraus, and Zschokke with cattle and pigs were almost equally favourable. Zschokke [76] considers it to be specially important from the point of view of the veterinary police that a subcutaneous tuberculin injection, given a few days before, exercises no influence upon the result of the intracutaneous reaction. This might otherwise be the means of frustrating the result of quarantine inoculation on the frontier. Klimmer, too, considers the intracutaneous reaction to be of service in cattle; but, according to his experience, the failures, as far as tubercular animals are concerned, amount to 25 to 30 per cent.

Without doubt the intracutaneous reaction is most unequivocal in the case of tubercular guinea-pigs. Klimmer, Kraus, Roemer, and Joseph are agreed as to this. Roemer recommends the injection of guinea-pigs with 20 c.mm. tuberculin in 0.1 c.c. fluid in the middle of a shaved piece of skin. Then, in experiments undertaken with Joseph, he observed that a more severe tubercular infection of the animal corresponded to a more severe intracutaneous tuberculin susceptibility.

**Esch's Method.** The extraordinarily characteristic intracutaneous reaction of a tubercular guinea-pig has been used by Esch [77] for the rapid detection of tubercle bacilli by animal experiment. The material to be examined is injected intraperitoneally or subcutaneously into two guinea-pigs, and after the ninth day following the injection both animals are alternately injected every third day with tuberculin intracutaneously. The dose used is 20 c.mm. in 0.1 c.c. of fluid. If the reaction is positive, the animal is killed so as to confirm the biological diagnosis by the anatomical. On the ground of his



comparative experiments. Esch considers this by far the most reliable and serviceable method of obtaining a rapid proof of the presence of tubercle bacilli. The method has proved useful in our own experience for tubercle bacilli in the urine.

Thus the intracutaneous tuberculin reaction is a useful means of diagnosis for veterinary purposes and of considerable assistance in experimental work on tubercular animals. Roemer and Joseph further deduce from their experimental investigations on animals that it is possible to ascertain quantitatively the hypersusceptibility of human beings infected with tuberculosis and probably possible to determine successfully whether, in individual cases, tubercular infection or disease exists. We cannot, however, at present share in this optimistic belief; first, because of the reasons which exist for not using the intracutaneous tuberculin test on man and also because of the same considerations which seem to show that the graduated cutaneous test of Ellermann-Erlandsen is unsuitable.

## 2.—THE CONJUNCTIVAL TUBERCULIN TEST.

The discovery of the conjunctival tuberculin test stands historically in close relation with v. Pirquet's cutaneous reaction and is associated with the names of Calmette and Wolff-Eisner. The former [78] calls it the "ophthalmic reaction," the latter [79] more appropriately the "conjunctival reaction," because the normal reaction takes place exclusively in the conjunctiva.

**Preparation of Tuberculin to be Used.** In the technique of the conjunctival reaction, the choice of the tuberculin is of great importance. Calmette recommends a tuberculin precipitated by 95 per cent. alcohol, the Calmette tuberculin test, made from bovine tubercle bacilli in the Pasteur Institute at Lille.

The fluid tuberculin test is obtained in sealed tubes; an ampulla available for 2-3 tests costs 1s. 6d., six ampullæ cost 7s. 6d. The dry preparation is obtained in little bottles of 5 mg., price 3s., and is sufficient, with the addition of ten drops of sterile water, for 10 reactions.

Calmette, with an experience of more than 10,000 patients, characterizes the reaction occurring with the tuberculin test (1 per cent. for adults,  $\frac{1}{2}$  per cent. for children) as without danger.

A different conclusion was arrived at by Goerlich, Siegrist, Wiens and Günther, Waldstein, Schille, Seligmann, Stülpe, Schiele, Barbier, Cohn, Klieneberger, Trousseau, v. Szabóky, Mitulescu and other writers, at home and abroad, who noticed



after instillation of a drop of  $\frac{1}{2}$  or 1 per cent. of Calmette's tuberculin test, even in quite healthy eyes, very disagreeable and often permanent injuries.

A preparation similar to Calmette's tuberculin test has been put on the market by the Farbwerke Höchst, under the name of "Tuberculosis Diagnosticum Höchst." It is a glycerin-free, dry tuberculin, obtained from Koch's old tuberculin.

**Tuberculosis  
Diagnosticum  
Höchst.**

The 0.1 per cent. solution of the Tuberculosis Diagnosticum is kept ready for use in glass tubes. Each tube contains sufficient for at least one reaction; six tubes cost 4s. 6d. The preparation in the form of powder in tubes containing 0.005 gr. costs 1s. 6d., and is to be diluted with 5 c.c. of cold sterile water before use.

But even this 0.1 per cent. Tuberculosis Diagnosticum Höchst is also described in many quarters as unreliable and very irritating. Koch's old tuberculin is the best and the cheapest preparation for the conjunctival test.

**Concentration.**

With regard to the concentration of the fluid for instillation, the most various propositions have been made. Our experience leads us to recommend for adults a 1 to 4 per cent., and for children a  $\frac{1}{2}$  to 1 per cent. dilution. Stronger concentrations are under no circumstances to be employed, whilst weaker ones are frequently inactive. The dilutions can be made by oneself (see page 70), with 0.5 per cent. phenol; they should be kept in a cool place and in the dark, and may be used as long as they remain absolutely clear.

**Use of other  
Preparations.**

Our attempts to replace old tuberculin by the albumose-free preparation were not satisfactory. For veterinary practice, Klimmer recommends phymatin (Humann and Teisler-Dohna's Chemical Works, Dresden) and bovotuberculol (Merck, Darmstadt). About 99 per cent. of tubercular cattle reacted to phymatin and 93 per cent. to bovotuberculol.

**Method of  
Installation.**

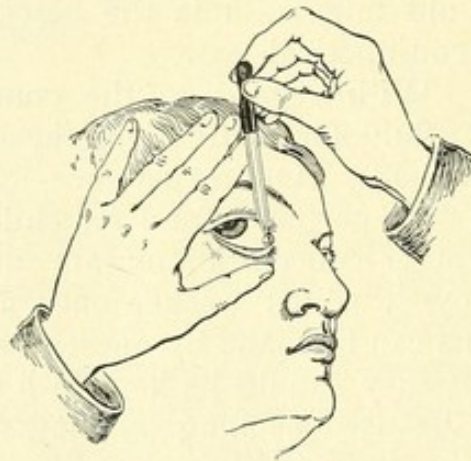
The technique of the conjunctival test consists of the instillation of the tuberculin dilution into the conjunctival sac. This must not be done till one is certain of the soundness of the eye from inquiry and careful examination. With the usual drop-pipette or drop-bottle, a single drop must be introduced into the conjunctival sac, care being taken that the drop is not immediately shot out again. In doing this, the pipette must not come into contact with the eye. On the other hand, care must be taken that the drop does not fall from too great a height



on the conjunctiva of the bulb, or even on the cornea itself, and thus give rise to pain and contraction of the lid as from the presence of a foreign body. The consequence would be either that the drop would be entirely shot out again or washed away by the reflex secretion of tears.

The instillation is most successful when the patient, sitting on a chair, inclines the head somewhat backwards. The operator, standing a little to the side and in front, draws down the lower lid, lets the drop fall gently into the conjunctival sac, as near as possible to the inner corner of the eye, and holds the lid for a short time retracted, so that the conjunctiva is well bathed with the solution. Then the patient is allowed to remain a moment longer with the eye looking up, without closing it.

Itching now and then occurs after the instillation and may



give rise to rubbing of the eye, unless this is expressly forbidden. A bandage to protect the eye is unnecessary, unless there is any reason to suspect malingering and an intentional simulation of traumatic irritation. For such exceptional cases a watch-glass bandage is to be recommended.

**Repetition of the** The disputed question must be considered  
**Instillation.** whether the instillation is to be done

once or repeatedly, and in the latter case whether in the same or the other eye.

The repetition of the instillation has been characterized as incorrect on the ground that the introduction of tuberculin into the conjunctival sac, even of clinically healthy subjects, gives rise to an artificial "physiological" hypersusceptibility of the conjunctiva, in consequence of which a positive reaction occurs on repetition. Theoretically this is possible; in practice the facts are that those persons who give a conjunctival reaction on repeti-



tion of the instillation may, indeed, be clinically healthy, but in point of fact are not free from tuberculosis and are really, in confirmation of the *post-mortem* results of Naegeli, Schmorl, Lubarsch, Hamburger, the subjects of a previous infection with tubercle, whether an inactive, obsolete lesion, or one merely quiescent. Our observations [59] agree in this, that persons really free from tuberculosis—a term, it may be observed, not synonymous with “clinically healthy”—give no conjunctival reaction, even when the instillation is repeated with 4 per cent. tuberculin any number of times on the same eye. Tuberculin, even when repeatedly instilled in the conjunctiva, cannot produce susceptibility in an organism perfectly, that is to say, anatomically free from tuberculosis. This is, moreover, borne out by the observation that the vast majority of new-born babes and infants show no conjunctival hypersusceptibility in spite of repeated instillations—they are really free from tuberculosis. Our experience shows that in adults only those can be considered free from tuberculosis who do not react to four graduated instillations (1 to 4 per cent.) in the same eye. Re-instillation is in itself not incorrect, but repetition in the same eye is doubtless more likely to reveal inactive and obsolete foci, which have no practical significance for the physician.

#### The Best Method.

Consideration of these facts suggests the following method: In adults, a drop of a 1 per cent. tuberculin dilution is introduced into the conjunctival sac, and if the result is negative the same process is repeated two days later on the other eye with a 4 per cent dilution. In children,  $\frac{1}{2}$  and 1 per cent. dilutions are used.

#### Control of Results.

The correct control and interpretation of the reaction is most important. This often begins in four to six hours, generally in twelve to twenty-four, reaches its acme in twenty-four to thirty-six hours, and remains visible three to four days, in exceptional cases six to eight days and even longer. Severe reactions occur, as a rule, within six hours, always within twenty-four hours; slighter ones tend to appear later and not to fade so soon that they are not apparent after eighteen to twenty-four hours. It follows that the instillation must be controlled twelve to twenty-four hours after it has been made.

#### Grades of Reaction.

The positive reaction consists in an inflammatory reaction of the conjunctiva, of which, with Citron [80], we can distinguish these grades:—

Grade 1.—Reddening of the caruncle and palpebral conjunctiva.



Grade 2.—Intenser reddening with involvement of the ocular conjunctiva, swelling and increased secretion.

Grade 3.—Intense reddening of the whole conjunctiva, severe chemosis, much fibrinous and purulent secretion and small ecchymoses.

A moderate reaction is shown on Plate II.

Observation must be very careful. The hyperæmia generally affects first and in characteristic manner the caruncle and semi-lunar fold. Severe reactions are easily recognized at a distance, moderate ones near to; and it is only with the slight reactive symptoms that it is necessary to get the patient to look upwards and outwards successively on the two sides, so that the two caruncles and folds may be accurately compared. In every case the lower lids are to be drawn down and compared, as the reaction may be limited to this part of the conjunctiva. When severe reactions of the palpebral conjunctiva occur the follicles tend to stand out more or less distinctly as glassy, swollen points.

**Specificity.** The specific nature of the reaction, which only occurs in the organism infected by tuberculosis, is seen to be highly probable from bedside and *post-mortem* observations. Specially conclusive are the experiences of v. Pirquet and Ganghofner with a large number of children, the indications given by the cutaneous test being confirmed *post mortem*. Sörgo has objected that cutaneous reactions to tuberculin as to other toxins—diphtheria, dysentery, cholera—are due to a common non-specific cause—a raised susceptibility of the cutaneous organs of tubercular patients. This is, however, refuted by the very careful experiments of Zieler [55].

**Nature of the Reaction; based on Hypersusceptibility.** The conjunctival reaction is a specific process dependent on the hypersusceptibility of the conjunctival tissues of tubercular individuals to tuberculin. It occurs on the basis of a local formation of antibodies, and is the expression of a local tissue reaction, rendered possible in the same way as v. Pirquet's cutaneous reaction, by the fact that the conjunctival tissue of tubercular subjects is in a condition of *allergie* towards tuberculin. That such a local formation of antibodies as a fact takes place has been proved by various authors under other conditions. Thus Leber has given a demonstration of specific antibodies in the aqueous humour in cases of ocular tuberculosis.

**Specificity.** It has been urged against the specificity of the conjunctival reaction that a positive reaction may occur also in the non-tubercular, in diabetics, in the



subjects of carcinoma, in the manifest stage of secondary syphilis, in scarlatina, acute rheumatism of the joints, enteritis, arthritis deformans, and acute bronchitis. In typhoid patients a percentage of even 50 per cent. of positive conjunctival reactions has been observed, with no clinical evidence of concurrent tubercular disease. From this the conclusion has been drawn of increased susceptibility of the organism to bacterial protoplasm in general, and the non-specificity of the conjunctival reaction deduced.

It seems to us that in all these cases the distinction has not been drawn sharply enough between "clinically non-tubercular" and "free from tubercle in an anatomical sense." Macroscopical examination is often alone insufficient to settle the vexed question, since tubercular changes may only be discovered on microscopical examination, or even only by animal experiment. Such confirmatory proofs are lacking in the observations given above, which state "tuberculosis *not present* on *post-mortem* examination" instead of "tuberculosis *not discovered*."

On the other hand, it must be remembered that sensitive eyes which sometimes respond with conjunctival irritation to the effect of draught, bright sunshine, terror, &c., also react conjunctivally to the irritation caused by the instillation of tuberculin without tubercular conditions being present. Moreover, now and then special conditions may be present in the eye, which may simulate a conjunctival reaction and give rise to a false diagnosis.

**Non-occurrence of Reaction.** In very cachectic patients and cases of phthisis just before death, the conjunctival reaction generally fails to appear. This is, however, in no way evidence against its specificity; rather is it obvious that in such individuals the ability to react to any stimulus whatever cannot be expected; even relatively large doses of tuberculin given subcutaneously are inert.

**Drawback to Value of Reaction.** In spite of its specificity, however, a great drawback to the diagnostic value of the conjunctival reaction in practice lies in the fact that a single instillation is quite insufficient in the initial stage of tuberculosis in which diagnosis is so difficult; and even when instillation is repeated in the other eye, the reaction only occurs in about half the cases of active initial tuberculosis.

It is evident from the observations of Klimmer and Kiessig [81] on tubercular cattle, that the definiteness and certainty of the conjunctival reaction depend on the concentration of the tuberculin. When 1 per cent. dilutions of the Höchst tuberculin were used no reaction took place; 5 and 10 per cent. dilutions did not always produce a reaction, and then merely a very slight one, only just perceptible. Even 20 per cent. dilutions did not always produce a reaction in tubercular animals. Reactions were only obtained with any considerable certainty by using 50 per cent. and pure tuberculin.

**Unreliability of the Method.** Thus by experiments on animals our assertion [59] is confirmed, that the conjunctival tuberculin test is unreliable in cases of



human phthisis, since the reaction may be negative in spite of the presence of *active* tuberculosis, just because 10 per cent. tuberculin and still stronger concentrations cannot be instilled into the eyes.

There is yet another defect in the diagnostic value of the conjunctival reaction. From the positive reaction on a single instillation the conclusion of active mischief is not justified, nor of an inactive focus from the positive reaction occurring only on repetition. The conjunctival reaction is therefore not suited for the determination of the activity of the disease. Moreover, the instillation of stronger or weaker concentrations does not allow of a differentiation: a case of active tuberculosis may only react on the second, third, or fourth instillation, and the clinically sound patient with inactive tuberculosis may react in typical manner to the first instillation. The number and concentration of the instillations necessary to call forth the conjunctival reaction, therefore, do not give even an approximate indication of the character of the tubercular process.

This standpoint is also supported by the numerous observations made by Klimmer and Kiessig [81] on tubercular cattle. Using 5, 10, and 20 per cent. dilutions of Höchst tuberculin, no special relation could be shown between the appearance of the ophthalmic reaction and the extent, age, and nature of the tubercular process. And to 50 or 100 per cent. Höchst tuberculin, as a rule, all tubercular animals reacted, whether the process were new or old, limited to a certain locality, or widespread, or generalized. This shows that the conjunctival reaction is not suited for discovering the activity of tuberculosis among cattle.

**Possible Harm of the Reaction.** Harmful action of the conjunctival test in its normal course, on the body as a whole, and on the general health, has not been observed, nor symptoms of general reaction. Subjective discomfort, such as photophobia, itching, burning lachrymation, as the feeling as of a foreign body in the eye—the last-named due to flakes of mucus—occurs, as a rule, only with the severer grades of reaction, and soon passes off.

But there are already recorded indisputable observations (Roemer, Kalt, Fehsenfeld, Schruppf, and others) of serious, persistent, and even the most severe disturbances of the eye in connection with the reaction. These were not due to faulty technique or to an unsuitable preparation, but solely to the introduction of 1 per cent. old tuberculin into the conjunctival sac, and are far more serious than a doctor, especially in private practice, should make himself responsible for (Wiens and Günther [82]).



**Two Grades of  
Mischief  
Distinguished.**

In relation to harm resulting from the conjunctival inoculation we recognize:—  
(1) The severe conjunctivitis following the instillation, with its highly unpleasant subjective symptoms.

(2) The local changes attended with actual danger to the eye. In order to avoid the former as far as possible the points already mentioned should be borne in mind, especially the use only of an absolutely clear old tuberculin dilution, 1 per cent. for adults and  $\frac{1}{2}$  per cent. for children for the first instillation; for the repetition in the other eye 4 per cent. and 1 per cent. dilutions respectively. Further, the following must be emphatically avoided:—

**Warnings.** (1) A second instillation in the same eye after positive reaction, no matter at what interval.

(2) A conjunctival instillation immediately after a subcutaneous tuberculin test.

(3) A subcutaneous tuberculin injection after a conjunctival reaction before the latter has completely disappeared, and that for several days. If (1) and (2) are not observed, very violent conjunctival irritation is created; if (3) is transgressed a recrudescence of the inflamed conjunctiva takes place.

**Recrudescence after Subcutaneous Injection.** The recrudescence of the conjunctival reaction after subcutaneous injection of the smallest doses of tuberculin is explained by the reactive combination of the remains of the tuberculin left behind in the conjunctiva with the antibodies newly formed by the subsequent injection, and is decidedly harmful to the treatment. M. Wolff [83] first drew attention to the fact that there are cases—and we ourselves have observed several of them—in which the conjunctival reaction recurs after every therapeutic injection of tuberculin, even with the smallest dose, sometimes most severely. Therefore we have repeatedly found ourselves obliged to cease tuberculin treatment altogether. That is a very weak point in the conjunctival method, because after establishing the diagnosis, it renders the most efficient treatment, that with tuberculin, unavailable. Wolff-Eisner [84] indeed looks upon this recrudescence of the conjunctival reaction as an advantage not possessed hitherto, “a measure for the doses to be used,” which are excessive when the reaction reappears, and considers the conjunctival reaction “decidedly advisable as a control of the treatment.” We cannot, however, accept this attempt to turn a disadvantage of the conjunctival reaction into an advantage.



In order, as far as possible, to avoid accidents which mean actual danger to the eye, every instillation must be preceded by a careful inspection of both eyes and inquiry after earlier ocular disease. But we must distinguish between absolute and relative contra-indication.

**Absolute  
Contra-indications  
in Eye Diseases.**

Absolute contra-indications are given by ocular disease, no matter of what kind and in what stage, even processes which have completely run their course, and in cases where one eye is sound and the other is or has been affected. To this category belong also follicular and trachomatous catarrh of the conjunctiva, which, according to Collin, Wien, and Günther, react to the instillation of tuberculin with symptoms of equal irritation and an abundant production of new follicles.

**In Infants and  
Scrofulous  
Patients.**

Absolute contra-indication is also given by such individuals as react more severely than the average, infants at the breast, young children and scrofulous patients of all ages. In scrofulous individuals all authors concur in noting the occurrence of phlyctenules and similar inflammatory phenomena. Even when these, as is the rule, pass off completely, they make medical treatment necessary, and may lead, without proper care, to serious and permanent affections of the eye.

**In Senility.**

Senility must also be looked upon as an absolute contra-indication, for then the cornea is much more liable to injury from severe reactions.

**Relative  
Contra-indications  
in Slight Affections  
of the Eye.**

Slight chronic hyperæmia which so frequently occurs and severe vascular injection of the conjunctiva must be considered as relative contra-indications. If these and similar conditions of the eye were reckoned as diseases, there would be so few healthy eyes remaining as to narrow the application of the reaction and make it quite insignificant for practice. But since simple and slight chronic irritation of the conjunctiva may now and then give rise to severe reactions, it is advisable to limit the diagnostic instillation in these patients as far as possible. This limitation is also advisable on the ground that chronic irritative conditions easily lead to misinterpretation of the result of the reaction, especially as there is an element of personal equation in judging a slight reaction.

**In Childhood.**

A relative contra-indication applies also to childhood in general. Various authors found in children such severe conjunctival reactions with intense congestion, inflammatory œdema, &c., that a serious condition arose. The instillation is also not easy to carry out in trouble-



some children, letting alone the fact that the dosage is very inexact and the result of the reaction correspondingly untrustworthy when the instillation only imperfectly succeeds, or when it is diluted or completely washed out by a flow of tears. Therefore with children we make our diagnosis by safer and quicker methods.

**Possibility of  
Simulation.**

Finally, the use of the conjunctival test is limited by the possibility of simulation. It is possible, at any time and without trouble, to simulate conjunctival reaction by artificially produced irritation, such as rubbing the inner surface of the lid with the fingernail or a match, and the result of such irritation cannot be distinguished in any way from a genuine normal reaction. This disadvantage has caused the medical department of the Prussian Ministry of War to reject this method for use in the Service by military doctors.

**Indications.**

The indications for the conjunctival test will be seen to be very limited; we shall refer to them later in speaking of the various localizations of tuberculosis. Here we will only make the general statement that it cannot be considered anything like so safe a diagnostic method as the cutaneous and percutaneous tests. Although, thanks to the greatest caution and the observation of numerous contra-indications, we have not as yet seen lasting injuries to the eyes, we do not consider ourselves justified in recommending the general use of the conjunctival reaction in medical practice. Over the head of the practitioner hovers, like the sword of Damocles, his sense of responsibility, and in this case more especially, for "the eye is the light of the body." He will therefore do well, as Schrupf [85] suggests, to get the consent of the patient before proceeding to the instillation of tuberculin, pointing out the possibility, even though it may not be very probable, of injury to the eye. We should certainly anticipate then that patients would with one accord decline the conjunctival test.

In private institutions (clinics, hospitals, sanatoria) it will not be necessary to take up quite this point of view as regards the conjunctival reaction, but its possible dangers must always be borne in mind, and in consequence it must only be used with special caution and careful selection when certain indications are present. In public institutes, too, the conjunctival tuberculin test should not be used under any circumstances merely for the purpose of scientific research.

**No Value in  
Prognosis.**

The conjunctival reaction has, according to our experience, no value in prognosis. We are not dissuaded from this opinion by the



publications of Meissen, Schuster, and Baer, who take their material from one institution alone and differ widely in their arguments without proving the prognostic value of the reaction. What *prognostic* help can be afforded by a test which gives a faulty *diagnostic* result in 50 per cent. of cases? That it is as good as no help at all was emphasized at the annual meeting of the British Medical Association in Belfast (1910) by Calmette himself, who has command of a very large material and would be the last to lower the value of his ophthalmic reaction.

**General Judgment  
of the  
Conjunctival Test.**

The general judgment of the conjunctival test may be summarized as follows: A negative result does not prove the absence of active tuberculosis. A positive result only proves the presence of a tubercular focus in the body of the patient without giving information as to its activity or inactivity.

We must expressly warn physicians against regarding the once repeated instillation as sufficient and its negative result as identical with "tubercle-free" or "inactive tubercle not demanding treatment at the time." Wolff-Eisner's [84] assertion that the conjunctival reaction, in contra-distinction to all other tuberculin tests, is the reaction of active tuberculosis has been and still remains refuted. And it would be a fatal backward step in diagnosis if Wolff-Eisner's estimate of the test were to be regarded as adequate even if only by a limited number of physicians.

In addition to its uncertainty, there is the possibility of serious harm. This renders the test unsuitable for general practice, or only admissible with certain reservations. In private institutions, too, it should only be employed with observation of definite absolute and relative contra-indications. As a rule the conjunctival test is only indicated when a therapeutic measure is dependent on its result, and definite reasons justify its preference to other diagnostic methods.

**Tuberculin  
Vaseline.**

Wolff-Eisner has recommended as a "modification of the conjunctival test in practice" the use of tuberculin vaseline. "With a sterilized glass tube a quantity of tuberculin ointment the size of a pea is introduced into the conjunctival sac, rubbing the ointment into the lower lid, which is drawn down, keeping the lids apart for about a minute by pulling down the lower lid with the finger." The reactions thus attained are said to be similar in appearance and course to the conjunctival reactions produced by liquid dilutions. The exceptional durability of the preparation is mentioned as a special advantage.



By this modification the conjunctival test is not freed from the odium resting upon it—in essentials it remains the same. Besides, it is unintelligible that Wolff-Eisner should, on the one hand, reject a dilution of tuberculin kept for eight days as too old and dangerous, and, on the other hand, declare that a tuberculin ointment has exceptional keeping powers, and is effective. In our opinion a  $\frac{1}{2}$  per cent. watery solution of carbolic acid is a much more reliable vehicle for tuberculin than vaseline.

After the failure of the tuberculin instillation it is not likely that a practitioner would be enticed into rubbing tuberculin ointment into the eyes of his patients. Nevertheless, we feel it our duty most expressly to warn all doctors against such a diagnostic manipulation. That "tuberculin vaseline" is more dangerous and unsuitable for the human eye than the instillation of tuberculin is evident, the method is more troublesome, the dosage—a quantity the size of a pea—quite inexact and control as to whether the ointment is good or not quite impossible. The conjunctival test "modified for practice" by means of tuberculin vaseline should be decisively rejected.

#### Nasal Reaction.

Lafite-Dupont and Molinier have recommended the Nasal Reaction (Rhino-reaction) as a substitute for the ophthalmo reaction, as it is free from risk and not visible externally. A swab of cotton-wool the size of a small lentil is dipped into a 1 per cent. dilution of Calmette's tuberculin and applied for ten minutes to the lower turbinal or the septum. After twelve to eighteen hours the reaction occurs, consisting of congestion and exudation of the part dabbed, and leads to the formation of a slightly bleeding scab, which lasts from four to eight days, and after peeling off leaves behind a slightly inflamed spot. There seems to be as little need for the Nasal Test as for the urethral, rectal, and vaginal tuberculin tests. The last-named is possibly of value in veterinary medicine; Richter recommends it for cattle.

### 3.—THE SUBCUTANEOUS TUBERCULIN TEST.

#### Selection of Tuberculin to be Employed.

The technique of the subcutaneous reaction is of the greatest importance if its full value is to be obtained and its disadvantages excluded. It will therefore be described in detail.

As a rule, only Koch's tuberculin (old tuberculin) is employed. For two years we have preferred Koch's albumose-free tuberculin, which, owing to the removal of the simultaneous toxic effect of the albumose, usually renders the general reactions much milder.



The bovine old tuberculin is less suitable for the purpose, Marmorek's serum and C. Spengler's IK quite unsuitable. The action of Rosenbach's and other tuberculins has not yet been sufficiently investigated.

### Preparation of Dilutions.

The tuberculin must be diluted, and this is done with  $\frac{1}{2}$  per cent. phenol solution and the dilutions kept in test-tubes which have been sterilized by boiling or passing through a flame, and closed with a cotton-wool plug, or in small sterilized bottles (10 c.c. in capacity) with wide necks and glass stoppers.

Besides the tuberculin itself, the  $\frac{1}{2}$  per cent. phenol solution and the sterile test-tubes, only two pipettes of 1 and 10 c.c. capacity accurately graduated into tenths or an accurate syringe are required to obtain accurate results.

### Authors' Method.

Only two dilutions are required for diagnosis: A 1 per cent. and a 1 per thousand. The 1 per cent. dilution is prepared by taking one division of the small pipette ( $= 0.1$ ) from the stock solution and 9.9 c.c. of  $\frac{1}{2}$  per cent. phenol with the large pipette, and mixing them in a test-tube. This dilution contains in 10 c.c. 100 c.mm. of tuberculin; in a 1 c.c. syringe 10 c.mm.; and in one division of the syringe 1 c.mm. of tuberculin. It should be labelled:—

No. 1. (Dilution 1 : 100)  
1 division = 1.0 c.mm. tuberculin.

From this 1 per cent. solution the other (or 1 per 1,000) is obtained by taking the small pipetteful of it and mixing in another test-tube with 9 c.c.  $\frac{1}{2}$  per cent. phenol. This contains in 10 c.c. 10 c.mm. of tuberculin; in a syringe 1 c.mm.; and in one division of the syringe 0.1 c.mm. of tuberculin. It should be labelled:—

No. 2. (Dilution 1 : 1,000)  
1 division = 0.1 c.mm. tuberculin.

In actual practice the procedure is as follows: Two sterilized test-tubes are labelled as above, and in No. 1 is placed 9.9 c.c., in No. 2, 9 c.c. of  $\frac{1}{2}$  per cent. phenol with the larger pipette. With the smaller pipette 0.1 c.c. tuberculin is taken from the stock bottle and mixed in No. 1; from this mixture 1 c.c. is taken with the same pipette and mixed in No. 2—the whole a work of a few moments.

According to the nomenclature in grammes and milligrammes formerly used, one division of No. 1 dilution ( $= 1$  c.mm.) contains 1 mg. and one division of No. 2 dilution ( $= 0.1$  c.mm.) a tenth of a milligramme of tuberculin.



**Dilution with the Syringe.** Dilutions may easily be prepared with the tuberculin syringe. We prefer the Lieberg tuberculin syringe with platinum-iridium needle, very accurately graduated, holding 1 c.c. and with a narrow lumen, so that the divisions be far apart. It is made entirely of glass, and, once sterilized and kept in carbolized water, it remains sterile, whilst the needle can be sterilized in a moment by heating in the flame.



The procedure is then as follows: One division (0.1 c.c.) of tuberculin is drawn up into the syringe and then nine divisions of diluting fluid ( $\frac{1}{2}$  per cent. carbolized water). The contents of the syringe are mixed by drawing the piston in and out and shaking. This gives Dilution 1, one division of which contains 10 c.mm. (10 mg.) of tuberculin.

If Dilution 2 is required, one division of Dilution 1 is retained in the syringe and nine divisions of carbolized water drawn up. The contents of the syringe are mixed; Dilution 2 is obtained, each division of which contains 1.0 c.mm. (1 mg.) of tuberculin.

Dilution 3 is obtained from Dilution 2 by retaining one division in the syringe and drawing up nine divisions of the diluting fluid, and the contents are mixed as before. One division of Dilution 3 contains 0.1 c.mm. ( $\frac{1}{10}$  mg.) of tuberculin. Thus any required diagnostic dose can be obtained direct from the syringe or placed in one of the small bottles or tubes and kept for future use.

When the dilutions are prepared according to the directions and placed in the dark in a cool place, they can be kept for several weeks. As a general rule, they can be used as long as they remain perfectly clear. Turbid solutions must always be discarded.

It is not advisable to have the tuberculin dilutions made up from prescription by the chemist on account of the high price charged. Besides, sterilized dilutions of old tuberculin are obtainable ready for use in hermetically closed glass tubes; the top of the capsule is broken off, the contents drawn up into the syringe and injected. It is well for those physicians who do not regularly employ diagnostic tuberculin to get the local chemist to keep in stock the sterilized injection doses which are required for diagnosis (0.2—1.0—5—10 c.mm.). It must be remembered,



however, that these dilutions become less active in course of time. The date of preparation should therefore be placed on the tube.

The subcutaneous injection of tuberculin prescribed by Koch has the advantage of the most exact dosage, which is necessary for tuberculin—the most potent drug in the whole Pharmacopœia for diagnosis.

**Method of  
Administration.**

In addition to the subcutaneous method, Mendel's intravenous method comes into question. In the action of tuberculin given by these two methods there is only a difference of time and degree; the reaction occurs much sooner and is far more marked by the intravenous method. But this is no advantage; on the contrary, the subcutaneous test is easier to perform and applicable to every case, *e.g.*, children and women with arm-veins difficult to make prominent. So what Koch [86] stated in his first publication, still holds to-day: "To obtain a reliable result, it (tuberculin) must be given subcutaneously."

**Technique of  
Administration.**

The injection is made under the skin, which should be rubbed with ether. The rapid insertion of the sharp needle is then almost painless.

**Site.**

The best site for injection is the back, below the level of shoulder-blades on a level with the last ribs and alternately on the two sides. In spite of aseptic precautions, it sometimes happens, especially if the reaction be severe, that there is a painful infiltration of the needle track, the so-called needle track reaction, which will be described later.

The arm is still often chosen as the site for injection. This may be more convenient, because the patient does not need to undress. Yet injections in the upper or lower arm are not to be recommended. They often result in very severe needle-track reactions, not infrequently in extensive infiltration, which hampers the free movements of the arm in a disagreeable manner. This may occur when no error in technique has been made or aseptic precautions overlooked. According to Schütz and Vidéky the local inflammatory irritability of the skin and of the subcutaneous connective tissue is greatest in the arm.

**Time.**

The best time for the injection is the early hours of the forenoon. It is not advisable to inject in the evening, because reactions may set in after six hours, pass unnoticed during sleep and have completely passed away by the following morning, with the result that the reaction escapes the notice of the physician also and the next dose is un-



necessary or too large. According to Hollmann [87], the tuberculin reaction commences four to eight hours sooner with morning injections than with evening; it almost always occurs during the day, a result of the action of light and of the increased metabolism by day.

Without exception an interval of at least forty-eight hours must be left between successive injections, as even considerable febrile reaction may set in after thirty hours.

**Range of  
Temperature  
Admissible.**

Before a diagnostic injection the range of the patient's normal temperature must be sufficiently known. For this purpose, two- or three-hourly observations of the temperature should be taken in the mouth—under the tongue, keeping the mouth carefully shut, for ten minutes—for at least three days in the case of patients with apparently normal temperature. The technique must be carefully explained to the patient and the temperature taken on the first occasion in the presence of the physician or the nurse; afterwards it can be taken by the patient himself with sufficient exactitude.

The maximum temperature at which a diagnostic injection can still be made was fixed by Koch at  $37^{\circ}$  C. He says: "The temperature should during a whole day, or better during two days, not range above  $37^{\circ}$  C." This limit should be retained with axillary temperature measurement, which we do not recommend on account of its uncertainty. With mouth temperature the upper limit may generally be put at  $37.2^{\circ}$  to  $37.3^{\circ}$  C. Patients with higher temperature must remain in bed until it has fallen to this limit, and after getting up it must still remain normal.

If the temperature has been artificially brought down to normal by antipyretic drugs, then the injection must not be made until the temperature has been quite normal for days without their use.

The best times for the three-hourly measurements are 8 and 11 a.m., and 2, 5, and 8 p.m., and it is important that the same times should be taken for the readings after injection, so that any variations which occur may be correctly interpreted. It is further advisable to instruct the patient to take his temperature at any other time that he may feel at all out of sorts; if necessary, at night. Four-hourly readings are insufficient.

In the female the time of the injection should not be so chosen that the reaction could be disturbed by the occurrence of premenstrual or menstrual fevers; and also, out of consideration for the patient's general health, these times should not be chosen for purposes of diagnosis.



The dosage of tuberculin given subcutaneously is different for adults and for children. We will first discuss the determining factors in adults.

**Dosage.** With regard to the size of the dose to begin and end with, there is as yet no general consensus of opinion. In the course of years a surprising number of methods have been evolved by different authors out of different clinical material, all having the same end in view—to choose doses large enough, but not too large. Koch's first instruction [86], which Beck [88] worked out on more than 2,500 cases, ran as follows: Begin with 1 c.mm. (1 mg.) tuberculin, increased to 5 and finally 10 c.mm. Later [89] he modified this procedure slightly and made it more precise: With weakly subjects begin with 0.1 c.mm.; with strong subjects, in whom only slight tubercular lesions are suspected, begin with 1 c.mm., increased to 5 c.mm., and then to 10 c.mm., repeated if necessary.

**Initial Dose.** With regard to the initial dose, opinion is now practically unanimous. A dose of 1.0 c.mm. (1 mg.) is unnecessarily large; smaller doses are sufficient, especially in the case of weakly or nervous individuals and in cases where a fresh infection is suspected, when a severe reaction is likely to occur. Too small a dose is, however, equally undesirable for physician and patient, as it only delays the decision. We recommend that the initial dose should be fixed at 0.2 c.mm. of tuberculin (2/10 mg.). (See Chart No. 1.)

**Increase of Dose.** Löwenstein and Kauffmann [90] proposed, in the case of patients who are going about, not to increase the dose at all, but to repeat the same small dose of 0.2 c.mm. four times within ten to twelve days, and so force a specific reaction; a proposal with much to recommend it.

The same standpoint was taken by Pickert, who limited himself to the repetition of small doses. There is the less need to discuss the theoretical basis of these proposals, as our own experiments—carried out independently of each other—have shown that neither of these methods gives reliable results. It is not the frequent repetition of the same small dose that is of decisive importance for the occurrence of reaction, but the size thereof, the actual quantity of tuberculin. The great majority of observers take the view that the difference between the increasing doses must not be too small, or a gradual tuberculin tolerance occurs even in the tubercular subject and leads to the non-appearance of reactions in spite of existing tuberculosis. This is illustrated with all clearness by the gradual process of tuberculin



treatment on the lines of Goetsch. For the production of reactions a sudden increase of dose is an absolute essential. On the other hand, too great differences between successive doses are not to be made, on account of the risk of severe reactions. The sequence of dosage recommended is then as follows: Increase from 0.2 c.mm. to 1 c.mm. for the second dose, to 5 c.mm. for the third, and finally to 10 c.mm. for the fourth and last. (See Charts 2, 3 and 4.)

**Phenomenon of  
Anaphylaxis.**

This method is also in accordance with the general view that four injections must be made before the presence of a tubercular process can be excluded. But against this repetition an argument has quite recently been raised on the ground of the phenomenon of anaphylaxis, that the repetition is itself a source of error.

Applied to the conditions of tuberculin diagnosis anaphylaxis might be caused by assimilation of the proteins contained in the tuberculin, and on repetition of the injection might produce the appearance of reactionary symptoms without tubercular infection being present. Theoretically that may be possible, but in practice the quantity of the foreign albuminous substances injected into the body is so small that the production of hypersusceptibility is quite improbable.

Then the hypersusceptibility towards the toxins of tuberculin would come into question in the sense that in healthy persons the toxins injected in the tuberculin create an anaphylaxis in consequence of which the second injection becomes positive. This is contradicted by the daily observation that the phenomenon of anaphylaxis fails to appear, in spite of repetition and increase of the dose of tuberculin, in the healthy, in a certain number of suspected cases, in non-tubercular pulmonary disease, and in earliest childhood (when other forms of reaction are easily produced)—clearly because in these cases there are no tubercular forms in the organism.

Finally the specific toxic hypersusceptibility of Wolff-Eisner is brought into the field against the repetition of the diagnostic injection of tuberculin. He says that the repetition of the subcutaneous injection which is in general use for the diagnosis of active tuberculosis is of no assistance. For the "stimulus" caused by the first injection is sufficient in cases of inactive tuberculosis also to cause a reaction on the repetition of the injection which cannot in any way be distinguished from that of the case of active tuberculosis. Those who wish to use the subcutaneous tuberculin test must make the dose of such a size that the *first* injection is followed by a reaction. The absolute impracticability of this proposal is evident. But apart from this, this purely speculative conception is contradicted by the practical results of nearly twenty years; in thousands of cases it has been proved that undoubted cases of tuberculosis in all stages do not react on the first injection of tuberculin, but do react on the second, or even perhaps not until the third or fourth dose.

We must therefore regard the attempt to discredit the tuberculin injection test (which has been proved successful a hundred



thousand times) by the suggestion of anaphylaxis as being entirely misguided. The repetition and increase of dose for diagnosis is correct and necessary.

**Precautions  
in Increasing  
Dose.**

In this connection it must be carefully borne in mind that the following dose may only be raised when the previous one has produced no rise of temperature. If the temperature has clearly risen, even by a few tenths of a degree, the dose must not be increased, but the same one repeated after the temperature has fallen quite to normal. (See Charts 5 and 6.)

The maxim to increase the dose only when the preceding one has been altogether without reaction is of importance in more than one direction. Firstly, it protects from the "tuberculin danger," which, if it occur now at all, is only observed by those who do not adhere to this simple and easily carried out rule. Secondly, the increasingly severe reaction after the repetition of the same dose is, according to Koch [86], "a phenomenon specially characteristic of the action of tuberculin, and may be regarded as an infallible indication of the presence of tuberculosis." Finally, in doubtful cases it may be taken as characteristic of a negative result when a slight rise of temperature disappears or is less marked after repetition of the same dose, and still more so after the next larger one.

It may then be taken as an axiom: Only increase the dose when the preceding injection has been borne without reaction; otherwise repeat the same dose.

**Maximal Dose.**

The acutest discussion centres round the question of the maximal dose, *i.e.*, the dose which, if borne without reaction, demonstrates the absence of tuberculosis.

Koch [89] fixed the limiting dose at 10 c.mm., which, for greater certainty, he was in the habit of giving twice; when no reaction results he held himself justified in assuming that "no recent or progressive tubercle" was present. On the ground of some hundreds of observations, we are content with a single maximal dose of 10 c.mm., others with one of 6 or of 5 c.mm., and even this is held by some to be too large. We cannot, then, yet speak of a generally accepted limiting dose with which the tubercular subject must react and the non-tubercular can not. It is more than doubtful whether such a limit could ever be determined with mathematical exactness. The occurrence of the tuberculin reaction as a biological phenomenon depends on the ability of the organism to react, and this again on the general constitution and on the local conditions for reaction present at



the moment. There are, however, as many different constitutions and as many different anatomical and pathological possibilities for the occurrence of the reaction as there are different individuals. The healthy human body is no constant quantity, and the tubercular subject is a highly variable one, making it altogether impossible to fix a maximal dose in diagnosis applicable to all cases.

Attempts have also been made, and we have ourselves tried for years, to draw conclusions about the activity or latency of the tubercular process from the dose which first produces a reaction. We have not been successful.

In our opinion the question about which dispute centres cannot be: What is the limiting dose in tuberculin diagnosis? But it must rather be put thus: With what quantity of tuberculin do we most nearly approach the limiting dose to which one must go to attain a specific reaction and beyond which the healthy individual also reacts?

Our own observations in this direction, extending over years, have shown that cases with clinical suspicion of tuberculosis, which quite failed to react to a final dose of less than 10 c.mm., showed later on well-marked tubercular foci at the suspected spots, with bacilli in the sputum.

In two further cases with positive history but doubtful physical signs, there was no reaction to 0·2, 1, and 5 c.mm. tuberculin, whereas the fourth injection of 10 c.mm. gave rise to typical reactions; the pulmonary foci which were then evident in both cases established their existence by the discovery of bacilli in the sputum. The reaction curve of such a case is illustrated by Chart 7.

Further reasons may be given for fixing the maximal dose at 10 c.mm. Wassermann and Bruck observed two cases in the initial stage which only reacted to 10 c.mm. of tuberculin; in both cases before the injection the examination of the serum showed the absence of any antibodies, whereas after the injection they were proved to be present. We, too, have repeatedly seen focal reactions which point to a fresh, active tubercular process, taking place only after the injection of 10 c.mm. of tuberculin, an observation which has lately been confirmed by the Tübingen Medical Clinic. (See Chart No. 8.)

It is a well-known fact that of recent cases a large proportion reacts to small doses of tuberculin with quick and generally pronounced rise of temperature, whilst older and less active processes frequently react only to higher doses, and this after a longer interval. However, considering the frequency of old,



dried up tubercular foci (especially in the tracheo-bronchial glands), it cannot be the aim of a diagnostic method to rake up such cases and make them submit to a course of treatment, the matter being mostly no longer of practical import. But this will certainly be promoted by the repetition of the maximal dose of 10 c.mm. of tuberculin.

#### Summary of Dosage.

The dosage in adults for the purposes of diagnosis may then be summarized thus :—

Initial dose	...	...	...	0.2 c.mm. ( $\frac{2}{10}$ mg.)
1st increase	...	...	...	1.0 c.mm. (1 mg.)
2nd increase	...	...	...	5.0 c.mm. (5 mg.)
Limiting dose	...	...	...	10.0 c.mm. (10 mg.)

#### Interpretation of Result.

But it must be noted that reaction to one of the tuberculin doses mentioned does not point with absolute certainty to *active* tuberculosis, requiring treatment. We are specially warned in this respect by the observations made during many years by Franz [93] on a thousand soldiers injected with tuberculin for purposes of diagnosis. In a Bosnian infantry regiment, which was recruited from a district infested with tuberculosis, 61 per cent. out of 400 recruits gave a positive reaction to subcutaneous doses of tuberculin up to 3 c.mm. In a Hungarian regiment from a neighbourhood where there was less tuberculosis, the percentage of reactions went down to 38 per cent.—a proof that the frequency of the tuberculin reaction coincides with the spread of tuberculosis among the inhabitants. Only those recruits were injected who, on clinical examination, showed no signs of disease in the individual organs. Only a small proportion of those in whom reaction took place suffered in the following years from clinically manifest tuberculosis, and moreover the Bosnian men more frequently (7.6 per cent.) than the Hungarian (3.2 per cent.), corresponding with the diagnostic figures. From these facts Franz rightly deduces that from the tuberculin reaction, that is, from the quantity of tuberculin necessary to produce the reaction and from the intensity of the symptoms of reaction, “no definite conclusions can be drawn as to the character and later development of the tubercular disease in Stadium I.” This conclusion of Franz is in complete accordance with what we have repeatedly emphasized for years, but which has certainly been overlooked by some physicians.



We will therefore repeat once more here: The subcutaneous tuberculin reaction, as such, tells us nothing certain as to the activity or inactivity of the process. It only tells us whether the person tested is infected with tuberculosis, which may be latent and active or latent and inactive. Whether the former or the latter is the case must be decided by clinical observation and by consideration of the history of the patient. Therefore the value of the tuberculin diagnosis will always remain conditional, no matter which of the tests is used, but the value of the subcutaneous test is much higher than that of the local tests, because the dosage is exact and the absorption of the injected tuberculin uniform. So after the experience of thousands of cases the conclusion may be drawn that several and increased doses may be necessary to show the presence of active tuberculosis, that with a dose of 10 c.mm. tuberculin and less, only those with tubercular foci react. We also know that rapid reaction to small subcutaneous doses of tuberculin denotes a more recent disease, delayed reaction to higher doses, older chronic processes. Between them there are various grades. And as the dividing line between active and inactive tuberculosis is by no means sharply drawn, but on the contrary is extraordinarily variable, the value of the tuberculin reaction, as being in itself and alone capable of proving the existence of active tuberculosis, is too schematic.

**Necessity  
of Careful  
Judgment.**

It would, however, be a crime against the spirit of diagnosis to let what has been said here prove an insurmountable barrier to the use of tuberculin. In biological reactions there is no rigid scheme, applicable to all cases; room must be left for the judgment of the physician in each individual case, of which the practitioner experienced in tuberculin will be able to take more advantage than the beginner. Thus it will be understood that in certain cases a third dose of 2.5 c.mm. and a final one of 5 c.mm. should be selected, *e.g.*, during the years of development in specially weakly persons, those who have a scare of consumption, excitable neurasthenics, and so on. The precaution should then be taken of keeping these patients under observation and in doubtful cases the diagnostic injections should be repeated.

**Safety of the  
Method.**

Hammer [94] and Junker [95] in their out-patient practice in the Heidelberg Hospital observed no important disturbance of health following the use of diagnostic tuberculin, and never any permanent damage or exacerbation of the tubercular process, and they therefore also agree that the use of tuberculin



injections in diagnosis is perfectly suitable for the general practitioner. Bulle [96], from his own experience, lays stress upon the fact that the use of tuberculin injections makes diagnosis much easier for the general practitioner and the club doctor.

### The Tuberculin Reaction.

The tuberculin reaction after subcutaneous injection is a specific reaction of hypersusceptibility on the part of the tubercular subject, just as is the case after cutaneous and conjunctival tuberculin inoculation. So that the phenomenon is uniform and the dissimilarities in the reactions are not qualitative but only quantitative, caused by the difference in dosage and the absolutely different conditions as regards the absorption of the tuberculin according to the site of application and the method used. Moreover, all tuberculin reactions essentially give results of equal value, which are modified in various ways by external causes (site of inoculation, dose of tuberculin, conditions of absorption).

Whereas the local tuberculin tests—used *lege artis*—take effect at the spot selected far from the real seat of the disease, the subcutaneous test attacks the diseased focus direct and in the end produces a focal reaction. The focal reaction is therefore the distinguishing and at the same time the most important characteristic of the subcutaneous tuberculin test, so important that from the diagnostic point of view the physical proof of the focal reaction, to which no exception can be taken, can be placed on an equal footing with the proof of the presence of tubercle bacilli.

### Its Nature.

The subcutaneous tuberculin reaction is made up of the following four components :

- (1) The rise of the temperature of the body (febrile reaction).
- (2) The disturbance of the physical well-being (general reaction).
- (3) The local inflammatory reaction at the site of injection (needle-track reaction).
- (4) The inflammatory reaction at the focus of the disease (focal reaction).

These reactions may appear all at the same time, or each separately, or several combined. The febrile and general reactions are the most regularly observed.

### The Febrile Reaction.

Fever is, of all the symptoms of the reaction, the most regular, the most objective and easily measured. In general a reaction is considered positive when there is a rise of at least  $0.5^{\circ}$  on the



highest temperature recorded before the injection. According to the height of the fever, the reaction is denoted as slight (up to  $38^{\circ}$ ), moderate (up to  $39^{\circ}$ ), or severe (over  $39^{\circ}$ ).

The beginning, height, and duration of the fever vary within such wide limits that it is not possible to speak of a typical reaction-curve. Most typical is rapid rise, slower fall, normal temperature reached after twenty-four hours or less often on the second day.

The rise of temperature begins on the average six to eight hours after the injection, but cases also occur in which it begins within four hours or is delayed for thirty. The acme of the reaction is reached on the average in about nine to twelve hours, whilst its duration may be thirty hours or longer, but several days' or weeks' fever is unusual. Uniformity is observable in so far as the smaller the dose of tuberculin administered, the later the reaction begins and the later it reaches its height.

#### **Cumulative Reaction.**

The rise of temperature is also as a rule slighter the smaller the dose. But cases are always occurring in which even the smallest doses produce rapid and considerable rise of temperature. It is, however, of practical importance not to construe a rise too rigidly. In view of the great instability of the body temperature, especially in suspected cases of tuberculosis, exercise, mental emotion, &c., may alone give rise to the half degree of variation, especially when they coincide with the physiological rise of temperature after meals or in the evening. Remembering the objection raised on the ground of the occurrence of anaphylaxis, there is now every reason to keep specially in the foreground the promptness and definiteness of the febrile reaction as the certain proof of the presence of a tubercular focus in the body. And in all cases where there is any doubt one should not be content with the half degree of elevation, but rather wait until the temperature has returned to the normal and then repeat the same dose. Then in active tuberculosis cumulative action almost always makes itself seen in the form of a more considerable rise of temperature (see Charts 5 and 10).

#### **Pseudo- reactions.**

Special note must be made of pseudo-reactions. These may now and then be due to intercurrent febrile affections, whose origin is not at once apparent, simulating a tuberculin reaction. We mention as an example a case in which an inflammatory swelling of the gums gave rise to a pseudo-reaction (see Chart No. 9).



The so-called psychogenic and suggestive rises of temperature belong to the same category. They occur in persons with signs of nervous instability—neurasthenics, hysterical persons, and those with erethitic constitution—and may be produced by the puncture of the needle or the injection of a few divisions of mere water (*injectio vacua*). Such cases are, however, by no means so frequent as to necessitate the injection of water in every case before the diagnostic dose of tuberculin is given in order to prevent the mistaking of a psychogenic for a specific reaction. It is only necessary to avoid verbal suggestions of any kind which in susceptible natures may cause fluctuations of temperature. When psychogenic fever is suspected, we recommend that the temperature be not taken by the patient himself and that an *injectio vacua* be given without his knowledge of its nature subsequently to the tuberculin injection. If fever then occurs, the first reaction was psychogenic; if there is no fever, the first tuberculin dose is repeated, and it is characteristic of cases of psychogenic reaction that the cumulative action on repetition does not occur. The diagnostic difficulties are such, however, that diagnosis of such cases should be left to a sanatorium (see Chart No. 10).

It must be added that in patients with nervous instability it is often impracticable to bring the temperature down to or below  $37.3^{\circ}$  C. (mouth). In such cases it is occasionally justifiable to proceed with the injection with temperatures of  $37.3^{\circ}$  to  $37.5^{\circ}$  C. (mouth).

#### **The General Reaction.**

The general reaction is the result of a toxic action on the human organism common to all bacterial products, and finds expression chiefly in a disturbance of the general condition. It follows from this that the quantity of tuberculin injected for diagnostic purposes must be such that on the one hand enough specific substance, on the other not too much toxic substance, is administered. According to R. Koch, the specific action of tuberculin is to be expected and in adults the toxic action excluded with a dose of 10 c.mm.

#### **Symptoms.**

Disturbance of the general health by various symptoms is the most regular accompaniment of the tuberculin reaction. The typical severe reaction begins with rigor and subsequent feeling of warmth, or with shivering and feeling of chilliness with malaise, giddiness, nausea or vomiting. At the height of the reaction the usual accompaniments are severe headache and pains in the limbs, pain of a dragging or stabbing character in the affected organ, palpitation, loss of appetite, thirst, sleeplessness, lassitude; in short, a general feeling of illness of greater or less



degree. With the fall of temperature, the symptoms give place to a feeling of general weakness, which, in its turn, usually passes off with return to normal temperature. The severest reactions mostly disappear in an incredibly short time.

With regard to the intensity of the symptoms there is great variability and it is not exclusively determined by the height of the reaction. Not infrequently, in spite of severe reaction, there is little feeling of illness; and, on the other hand, with slight febrile reaction the whole gamut of symptoms enumerated may be complained of. In this respect individual differences and susceptibilities play a great part and occasion the incidence of symptoms in various organs, *e.g.*, gastric and intestinal symptoms, disturbances of the bladder, of the central nervous system, sensory or motor, &c. To the most frequent objective symptoms belong acceleration of the pulse and respiration.

In the urine, albumin may very occasionally be present as a febrile symptom. The rare occurrence of loss of consciousness, of stupor, of swelling of the spleen or of the lymph glands in the region of the injection, need only be mentioned.

**Local  
Reaction.**

The needle-track reaction at the place of injection, a local infiltration of the subcutaneous tissues, is the most frequent objective symptom, and consists of swelling and painfulness at the injection site. When old tuberculin is employed, a more or less distinct local infiltration occurs with such regularity with every positive tuberculin reaction that its non-occurrence almost points to a pseudo-reaction. With albumose-free tuberculin, the needle-track reaction is decidedly less frequent and less severe, often invisible and only signalized by slight painfulness.

**Focal  
Reaction.**

The focal reaction has an advantage over the febrile, general and local reactions in that it gives a clue to the site of the tubercular process in the body. Certain phenomena in the sequelæ of the reaction have a significance in localizing the disease, *e.g.*, spinalgia or tenderness over the spinous processes and the sternum, associated with a feeling of tension in the chest, may be caused by increase in the intra-thoracic pressure from swelling of the thoracic lymph glands, a focal reaction. Disturbances of heart and stomach may be referred to direct irritation of the vagus, also from lymph glands in a state of inflammatory reaction.

In fine, every individual focal reaction which remains limited to the tubercular process and has the course of a fleeting inflammatory affection will give rise to different symptoms, according



to the structure and function of the particular organ with which it is connected. On this rests, in no small degree, the advantage of the subcutaneous administration. In the Special Part, we shall return to the most noteworthy symptoms in connection with the several organs.

**Treatment  
of the  
Reaction,**

Special treatment of the tuberculin reaction is, as a rule, unnecessary. The condition of the patient determines whether rest in bed is necessary or not; there is no justification for the measure of confining him to bed during the whole period of the injections. For severe headache, in addition to the ice-bag, phenacetin, antipyrin, antifebrin, lactophenin (0.25 to 0.5 grm. once or more) or migranin (1 grm. once or twice) may be given; for very high fever small doses of pyramidon (0.1 grm., repeatedly). In general, drugs should not be given until the highest point of the temperature curve appears to have been passed.

**of Special  
Symptoms.**

Special symptoms require, when necessary, their appropriate treatment: *e.g.*, sleeplessness with bromide, bornyval, dormiol, veronal, or adalin; intestinal disturbance with opium, bismuth or calomel. The subject of a reaction is certainly a sick person, but one who soon recovers. After the reaction has passed off, the patient often shows and acknowledges a special feeling of well-being, a fact noted by R. Koch in his first publication, and which is brought about by the removal of toxins from the organism in general and the consequent improvement or even complete disappearance of all kinds of complaints which had chiefly been referred to the diseased focus. This happens most frequently after severe reactions.

Saathoff [97] discovered by very careful metabolic experiments that in the tuberculin reactions, besides the feeling of general well-being after the fall of temperature, there is almost always during the reactionary stage, in spite of the fever, a rapid and lasting increase in weight, which he attributes in the main to a diminution in the processes of combustion in the body, to the retention of water and deposits of salt. He concludes from this that the tuberculin reaction brings about a very great change in metabolism, especially in mineral metabolism, and by so doing leads to a distinct turn for the better in the course of the disease. We can confirm this from the observation of 300 to 400 cases annually. Increases in weight of two, three and more kilogrammes are the regular thing during the diagnostic use of tuberculin; no increase or a decrease is quite exceptional. And in many cases we also have had the impression that even by the first tuberculin reaction we have materially benefited the patient. This is also quite in conformity with the observations made by Hager, Longard and others, especially in anæmic and chlorotic girls and in those suffering from gastric troubles, suspected of tuberculosis.



We have not observed serious or permanent harm even after the severest tuberculin reaction, above all no permanent disturbance of the functions of the heart, the lungs, the pleura, the kidneys, or nervous system. Basing our opinion on the observation of several thousands of tuberculin reactions, we would specially emphasize the point and advise the critical consideration of every individual case without adopting straightway the lay point of view that a *post hoc* proves also a *propter hoc*. This warning seems specially necessary in view of the statements of Ulrici at the sixth Congress of Sanatorium Physicians; we shall return to this in the Special Section.

**Contra-indications :** Contra-indications can be specially sharply enunciated now that we have other diagnostic methods giving only a *local* reaction. Although after countless observations the phrases "generalization of the tubercular poison" or "mobilization of a hostile army" have become devoid of all foundation, yet the precept "*primum nihil nocere*" remains of the first import to the diagnostician. He must first of all decide what are the conditions which, under all circumstances, contra-indicate the diagnostic use of tuberculin.

**(1) Fever.** The first contra-indication and the one occurring most frequently in practice is a rise of temperature above  $37^{\circ}$  C. in the axilla or above  $37.3^{\circ}$  C. in the mouth. This is based on the consideration that a variable temperature above the normal limit renders impossible a proper estimation of the significance of a febrile reaction after the injection. And besides this, reactive processes taking place in the system and giving rise to fever disturb the action of the tuberculin. Only in subjects of unstable temperament—nervous, neurasthenic, hysterical and erethitic patients and those with a morbid dread of tuberculosis—may exception be made; even then the temperature must not exceed  $37.5^{\circ}$  C. nor be referable to the focus which raises the suspicion of tuberculosis.

**(2) Diagnosis Certain on other Grounds.** Secondly, tuberculin is contra-indicated in diagnosis in patients where the clinical history or the physical signs alone make the diagnosis certain, and where tubercle bacilli are present in the sputum. Tuberculin diagnosis is generally superfluous in these cases. The clinical history must be taken and physical examination carried out with the utmost care as well as repeated examinations of the sputum made (antiformin method, Gram-staining, &c.) before the syringe is resorted to. It would be a perversion to see in the tuberculin reaction a



convenient way of avoiding the well-tried older methods. "Not in the alternative use, but in the combination of the various methods of clinical examination, lies the value of additions to our diagnostic armament." Tuberculin is not designed to replace but to supplement the other approved methods of physical diagnosis, and to enter the field when they fail. The subcutaneous tuberculin test is a single aid to diagnosis and the last to be employed.

Thirdly, recent hæmoptysis in cases of suspected pulmonary tuberculosis is a contra-indication. The possibility of the occurrence of a hæmoptysis following on the rapidly rising dosage of diagnostic tuberculin must be admitted. A violent local reaction may cause destruction of tubercular tissue and hence increase the likelihood of blood being effused. The stronger cough effort which may occur during the reaction must also be considered, and the possibility of severe hæmoptysis is made greater. It will generally be impossible to decide whether *post hoc* or *propter hoc*, but the occurrence of a considerable hæmorrhage is an event of such serious moment that everything must be scrupulously avoided which might tend in this direction. In cases, therefore, where the sputum contains even traces of blood, rest in bed should be prescribed until these have disappeared, and only after several days out of bed without the blood returning should tuberculin diagnosis be commenced; and then with great care, and only as a last resort to establish a diagnosis.

The physician should always assure himself personally of the character of the sputum; exaggeration and concealment are frequent in this respect, even without intention of bad faith. Fairly often the appearance and smell of the blood-stained sputum will leave no doubt that the blood has its origin in neglected gums or in chronic inflammatory conditions of larynx, pharynx, or naso-pharynx. Here, of course, there is no contra-indication. On the other hand, the blood coughed up may have the characteristics of a hæmoptysis, and then the clinical history and physical signs will as a rule assure the diagnosis.

#### (4) Heart Disease.

Fourthly, heart disease. When it is borne in mind that in isolated cases the tuberculin reaction itself has resulted in conditions of angina pectoris, precordial distress, dilatation of the ventricles and irregularity or dicrotism of the pulse, a sound or, at any rate, functionally perfect heart must be held to be a *sine quâ non* of tuberculin diagnosis. Slight disturbances of the heart's action, especially those of a functional nature, occur so frequently with early tubercle that on practical grounds alone they should not



exclude the application of the method. And in practice this is altogether unnecessary. But severe valvular disease, and conditions such as myocarditis, fatty or weak heart contra-indicate this method of diagnosis.

(5) Renal  
Disease.

Fifthly, renal disease. Even in patients with sound kidneys albuminuria may occur, but seldom, at the height of the tuberculin reaction; this is a transitory febrile phenomenon and therefore of no significance. It is also possible that this passing albuminuria is connected with the lowered systolic and raised diastolic blood-pressure seen after tuberculin injections. Reznicek's [98] experiments show that in chronic renal inflammation the systolic pressure is considerably reduced even by small tuberculin doses. Therefore, in cases of existing renal disease of non-tubercular nature, serious damage may occur as a sequel to the tuberculin reaction; *e.g.*, increase of albumin, of casts and other formed elements, hæmaturia, &c. Hence an examination of the urine must precede the application of the method, and any form of nephritis be held to contra-indicate it.

(6) Epilepsy.

Sixthly, epilepsy. The possibility of the irritative action of the tuberculin reaction on the *locus minoris resistentiæ* of the epileptic cannot be gainsaid; and in actual fact it has been observed that after being absent for years epileptiform seizures may occur as a sequel to the injection. Epileptics suspected of tuberculosis should not be exposed to this risk; the method must be abandoned.

(7) Hysteria as a  
Contra-  
indication.

Hysteria and severe neurasthenia may also be regarded as contra-indications now that we possess the local tuberculin tests, since in a considerable percentage of cases a tuberculin reaction may be simulated by oscillations of temperature due purely to psychical causes and without tuberculosis being present. But here too when the local tests give a doubtful result the subcutaneous injection comes into its rights; only, for the reasons given, it must be carefully and critically done and control injections of water given.

(8) General  
Contra-  
indications.

Finally, the tuberculin reaction is contra-indicated, from reasons of expediency as well as on scientific grounds, where miliary tuberculosis is suspected, since its downward course might be accelerated; where there is suspicion of intestinal tuberculosis, and the presence of deep intestinal ulcers can be deduced from special areas of tenderness to which the



resulting localized peritonitis has given rise; in convalescents and weakly persons immediately after severe diseases (typhoid, scarlatina, pneumonia, pleurisy, peritonitis, perityphlitis, gastric ulcer, &c.); and finally in patients with severe diabetes, tendency to apoplexy, marked arteriosclerosis or amyloid degeneration of the abdominal viscera.

#### Indications.

The indications for the subcutaneous application of tuberculin in diagnosis are in general: (a) To make an early diagnosis in doubtful cases; (b) to determine the course of treatment where difficulty in making a differential diagnosis is present.

This general statement as to the indications may, apart from the contra-indications already mentioned, now be limited in the direction of leaving the subcutaneous test to the last, whilst it remains the most certain of the methods. It decides in cases where a focal reaction gives promise of help in localization, and where the cutaneous, percutaneous, or conjunctival tests are contra-indicated or lead to no certain result.

We especially emphasize here this diagnostic importance of the subcutaneous tuberculin test, because it has been done away with at the veterinary stations on the frontier and at the veterinary quarantine stations. This might give rise to the impression that tuberculin had proved a failure in diagnosis. But this is not the case. On the contrary, according to Schütz [99], the official tests by Casper and Olt on the cattle imported from Denmark show that only 2 to 3 per cent. of animals which reacted in the prescribed manner to the injection of tuberculin and were slaughtered showed no traces of tubercular changes. "Consequently tuberculin can be looked upon as an almost infallible means of determining the presence of tuberculosis in cattle" (Schütz). The chief reason why this method, which even in very high doses never involved any danger to the animal inoculated, has been officially abandoned is this: that the cattle dealers, shortly before the official test, gave tuberculin injections on their own account. By this means they were able to establish a certain degree of tuberculin tolerance and in increasing measure deprive the official test of its value. It remains to be seen whether the veterinary tuberculin diagnosis in frontier and quarantine stations will be permanently abandoned. We fear that the abolition of the tuberculin tests will only help to promote the importation of tubercular cattle from other countries. The subcutaneous tuberculin reaction (also called the "thermal" reaction in veterinary medicine) gives useful results also in the diagnosis of tuberculosis in horses, sheep, goats, pigs, dogs, rabbits, and guinea-pigs; it only fails in fowls and turkeys.

#### The Method in the Case of Children.

In children the doses of tuberculin for the adult are to be reduced by one-half: begin with 0.1 c.mm., increase to 0.5 c.mm., then to 2.5 c.mm., and finally to 5 c.mm.

Engel [100] urges against this dosage that the decrease in the



dose for children is not justified, because the susceptibility to tuberculin depends on the extent of the tubercular process and not on the age of the particular subject, and that the typical children's tuberculosis is characterized by great tolerance of tuberculin. He is right in both statements; but this will not lead us to fix the tuberculin dose for purposes of diagnosis at the same height as for adults. For in the first place a larger dose may produce a purely toxic action. And secondly, we do not know before the injection of tuberculin whether it is a case of tuberculosis, let alone a case of typical children's tuberculosis, very tolerant of tuberculin. It is also in keeping with our pharmacological views to give a smaller dose of a toxic substance to a child than to an adult. We therefore stand to our proposal to give children as a first diagnostic injection of tuberculin a dose not larger than .01 c.mm. and the fourth and last dose not larger than 5 c.mm.

The high diagnostic value of tuberculin injections and their absolute safety are, according to the observations of Binswanger [101], most marked in youth. Of 261 children whom he injected thirty-five reacted, and of the total number forty-two were examined later *post-mortem*. Sixteen who had reacted were all tubercular; of twenty-six who had failed to react, twenty-five were found free from tubercle, and only one had any signs of tuberculosis. The latter case, moreover, does not tell against the certainty of the method, as the injections were made in the fifth week of life, when doubtless infection had already taken place, but no tubercular lesion was yet present.

Tuberculin is, then, a reagent for the detection of tubercular disease, not for tubercular infection without anatomical change. The so-called resistance of the healthy suckling is nothing but the expression of "the suckling's freedom from tubercle in an anatomical sense."

Although most of the children injected by Binswanger were in the first year of life, not one of the thousand individual injections led to any bad result. It would be unfair to demand from a diagnostic method greater harmlessness and certainty than this.

The general judgment of the subcutaneous test can be summed up as follows: After childhood, it is the sovereign diagnostic method and renders possible the early diagnosis of tuberculosis in all its localizations and forms. Its advantages far outweigh its disadvantages; it is specially valuable in view of its diagnostic certainty. It is applicable to ambulant practice, and with sufficient care the results of reactions are harmless. All harmful

#### Conclusions.



results can with certainty be excluded if the cases are properly selected, indications and contra-indications observed and a scrupulous technique employed.

### Needle-track

### Reaction of Escherich.

A further reduction of the dose of tuberculin used for diagnosis in children is made in the needle-track reaction of Escherich [102].

This is nothing else than an allergic test of the subcutaneous tissue, an abbreviated subcutaneous test occurring with a small dose of tuberculin and not leading to general reaction.

### The Method.

Reuschel [103] recommends the following procedure: a dilution of old tuberculin is prepared with 0.85 per cent. saline which contains 0.5 c.mm. of tuberculin in 1 c.c., and a first dose of 0.2 c.mm. is injected on the inner side of the forearm. In practice, therefore, four divisions of a 0.1 in 200 dilution of tuberculin are used.

If the reaction is positive, inflammation arises in the subcutaneous tissue and is projected on the surface of the skin as a sharply circumscribed red spot, quite distinct from a red areola around the puncture, which is not characteristic. Besides the reddening, there is, as a rule, infiltration due to œdema and great tenderness. The symptoms generally increase in the first twenty-four hours, reach their maximum in forty-eight, and begin to pass off in the course of four to ten days, according to their intensity. With indistinct reaction and no general disturbance the dose should be doubled.

The method of the needle-track reaction fails, according to Reuschel, in cases of severe cachexia, and generally in children with miliary tuberculosis. But it affords a possibility of applying a specific test to children in spite of existing fever and of testing the specific import of temperature oscillations after an injection. Fever without needle-track reaction would be suspicious of non-specific origin.

Finally, the reaction makes it possible to control the results of v. Pirquet's cutaneous test in doubtful cases. Hamburger [104] places this indication in the front, for it is unsatisfactory that in cases of active children's tuberculosis no cutaneous reaction should take place and thus lead the diagnosis astray. In such doubtful cases in children (when from clinical examination tuberculosis is suspected and the cutaneous test is negative) then the needle-track reaction should be tried by injecting during the next two or three days 0.1 to 1.0 c.mm. of old tuberculin. If a



positive needle-track reaction then takes place, which is generally unaccompanied by any severe febrile and general symptoms, then it may be assumed with certainty that there is a tubercular focus. According to Hamburger's observations, the needle-track reaction failed so very seldom in cases of active tuberculosis in children that he considers it the best of all the tests for children.

**Value of Escherich's Reaction Limited.** We can only give conditional approval of the needle-track reaction as a means of diagnosis of children's tuberculosis. It is not absolutely trustworthy. Moreover, the dose for the first injection proposed by Reuschel (0.2 c.mm.) seems to us too high. It will now and then call forth violent general reactions with high fever, which may become serious in the case of children already febrile. A strict contra-indication to the subcutaneous injection of tuberculin for purposes of diagnosis is given by fever. And this must be adhered to under all circumstances. We must therefore warn against the subcutaneous injection of Reuschel's proposed dose of tuberculin in febrile children for the purpose of observing the needle-track reaction. Hamburger's proposal, too, only to have recourse to the needle-track reaction after the cutaneous inoculation has proved negative, is only to be accepted with the proviso that the children have no fever. Hamburger himself has observed that tubercular children will sometimes react to .001 c.mm. of tuberculin and even to smaller doses.

For the rest, both in children and in adults the needle-track reaction may be useful in all those cases where the subcutaneous test has been used, so far as the appearance and condition of the site of inoculation may enhance the value of the diagnosis. If a needle-track reaction takes place without simultaneous general reaction, one concludes that there is hypersusceptibility of the skin to tuberculin, and will either not increase at all or only very slightly increase the next diagnostic dose of tuberculin. If the condition of the site of injection agrees with the result of the general tuberculin reaction, this agreement points all the more certainly to the presence of tuberculosis. And finally, in those cases in which the tuberculin reaction is doubtful, the positive needle-track reaction may be able to turn the scale and to cause us to refrain, specially in the case of children, from continuing the injections until a well-marked tuberculin reaction occurs.

With adults the needle-track reaction by itself is of no value for diagnostic purposes. Injections of 0.2—1—5 and 10 c.mm. of tuberculin may lead to severe needle-track reactions, without any general tuberculin reaction at all. With adults the needle-



track reaction is evidently too severe, much more so than the cutaneous reaction. On the other hand a negative needle-track reaction with simultaneous increase of temperature suggests that the fever is not of specific origin but psychogenic or purposely simulated. We come across many such cases.

So in dealing with children the needle-track reaction has this importance—it controls or confirms a negative cutaneous reaction in the case of tubercular suspects. In this respect it competes with the intracutaneous test, which should always be preferred in febrile conditions.

Besides, the needle-track reaction may assist in interpreting the results of the subcutaneous test both in children and adults.

Fever is a contra-indication of the needle-track reaction both in adults and especially in children.

Tedeschi recommends the lobe of the ear as the site of the needle-track reaction. We, with Montis, reject it, because this "auricular reaction" leads to disfigurement and sometimes to swelling of the retro-auricular glands, without offering any special advantage. It is, at the least, an unnecessary measure to adopt.



## B.—Special Section.

HAVING described the various tuberculin tests and their application, we come now to the special features which may in any particular case lead to the preference of one or another method or a combination of several. We have nowadays the indisputable advantage of not being limited exclusively to the subcutaneous method; by the discovery of the local tests the diagnostic method has been extended and the opportunity given for accurate dosage and for individualizing. Of this advantage we must make full use, but it must not be forgotten that none of the tests give a direct proof of existing tubercular disease, but only prove the presence of a specific reactionary body which presupposes the existence of tubercle toxin in the body. Therefore in each individual case from the result of the test in combination with the clinical facts and the patient's own statements, the doctor has to devote special consideration to decide where the tubercular focus is situated in the body, and whether it is a tubercular *infection* or tubercular *disease*. The following section will lay down the lines on which this can be done.

For practical convenience the methods in adults will first be discussed under the various localizations, and then a special section devoted to diagnosis in children.

### 1.—TUBERCULIN DIAGNOSIS IN TUBERCULOSIS OF THE LUNG.

Pulmonary tuberculosis merits detailed discussion on account of its frequency and the special importance and difficulty of its early diagnosis.

Diagnosis easy  
in well-marked  
Cases.

The clinical picture of well-marked pulmonary tuberculosis is practically always and without difficulty to be recognized by physical examination and furthermore, in most cases, by demonstration of tubercle bacilli in the sputum. But if the clinical history is uncertain and the physical signs doubtful, or if the history indicates phthisis and yet the signs are negative, the question whether tubercular disease is present or not is difficult to decide. Bacteriological diagnosis in these cases generally fails in spite of the modern antiformin method, either because there is no secretion from the lungs or because the secretion contains no tubercle bacilli.



**Tuberculin necessary in Doubtful Cases,** As long as tuberculosis of the lungs is such a universal disease, the practitioner will be constantly meeting such cases, and will diagnose them wrongly or not at all, if the last, the best and the keenest diagnostic agent, the injection of tuberculin, be not employed and its result considered along with clinical observation.

**and to establish an Early Diagnosis ;** Many physicians, it is true, still believe that clinical and bacteriological methods alone are sufficient, but surely to-day there are but few hospital doctors who do not admit the special value of tuberculin diagnosis in the early stage of pulmonary tuberculosis. In any case, without the help of tuberculin it must repeatedly happen that a case of pulmonary tuberculosis is only diagnosed when the best moment to effect a certain, rapid, and permanent cure is past, or cases are treated as tubercular which have nothing in common with tuberculosis. Over 50 per cent. of the cases sent to sanatoria are already in the second and third stadium of pulmonary tuberculosis and 5 to 8 per cent. are not tubercular at all !

Trifling physical signs, such as slight retraction of one apex, slight alteration of percussion note at one or both apices, slight flattening of the chest on one side, indistinct lagging, slight weakening or roughening of the inspiratory murmur, systolic cogwheel breathing (localized), prolonged expiration, occasional inconstant rhonchi, or constant but limited to a spot not exactly at the apex—all these will not be missed by the practised observer, but will often not suffice to establish the diagnosis of commencing pulmonary tuberculosis.

**to confirm Doubtful Physical Signs.** In addition there are not infrequently anomalies of structure or function producing differences in percussion and auscultation without the underlying lung being affected. These are slight scoliosis in the cervical or dorsal region, unilateral muscular hypertrophy, dropping of the right shoulder, differences in the course or branching of the upper bronchi, &c.

Examination with the Röntgen rays, also, in many cases does not remove the difficulties of diagnosis ; catarrh alone is certainly not shown ; by some accident or other, slight thickenings may not be shown or an appearance of opaqueness in the apex may simulate the beginnings of an affection of the lung. As to whether shadows denote fresh or healed infiltration, calcareous induration, scars or puckered nodules, Röntgen-ray examination gives



no clue. Even the Kreuzfuchs improved technique with the astral screen affords no certain diagnostic, much less differential diagnostic aid in the recognition of apical changes; there is still no agreement as to the striations running from hilus to apex.

So there are doubts. And even when physical examination and the use of the Röntgen rays give the most accurate information as to the site and extent of the disease, they tell us nothing of the etiology of the pulmonary foci. In all cases where tuberculosis is suspected, specific diagnosis is necessary, so that timely treatment may be commenced. Here we entirely agree with Penzoldt [105], for want of clearness on the part of the physician and uncertainty on the part of the patient are much more frequently responsible for the incurable cases than the latter's neglect to consult the doctor in time.

The grounds which formerly prevented the medical man in private practice from using tuberculin in diagnosis are done away with now that it is possible to use tuberculin with ease and safety. Exceptions apart, every practitioner should now be in a position to test any doubtful case with tuberculin, provided he is successful in overcoming any possible opposition on the part of the patient by pointing out the safety and necessity of the tuberculin tests. Then also in private sanatoria, the advanced stages of pulmonary tuberculosis will give place to those of more favourable prognosis, still curable.

In hospital practice the indication for tuberculin diagnosis is present for all clinically doubtful cases. The decision to wait until the physical signs are more distinct is too unscientific from the physician's point of view and too risky for the patient. The salvation of cases of pulmonary tuberculosis belonging to the working class is the earliest possible diagnosis. And as our public hospitals are in duty bound to diagnose as far as possible all cases of pulmonary tuberculosis at the commencement of the disease and when necessary to submit them to an expensive course of treatment, tuberculin diagnosis has become an integral part of the equipment of the hospital physician.

And lastly, in sanatoria it is a necessary part of their activity to make certain of the diagnosis in view of the many attacks on their results. The opponents of sanatoria will be robbed of one of their most potent weapons when it is proved beyond question that the lung affections of sanatorium patients are, in actual fact, of a tubercular nature.



And further, however scrupulous the cleanliness and the observation of rules for coughing and spitting in the sanatorium, there is, in view of the indisputable correctness of the theory of spray infection, an increased risk in prolonged and intimate relation with tubercular subjects for those with unsound lungs specially susceptible to tubercle bacilli. Hence the exclusion of the non-tubercular from the sanatorium must be insisted on.

Furthermore, the not inconsiderable cost of treatment in a sanatorium forbids making it accessible to those in whom no tubercular disease is present and in whom life and the ability to work are not threatened. At the least it would be a hardship to withdraw a non-tubercular case for three months or more from his family and occupation. Hence therapeutic, practical, hygienic and social grounds all combine to make the employment of tuberculin diagnosis essential in the sanatorium. The armoury of diagnostic weapons is incomplete without it, as it will confirm or exclude a clinically doubtful case of pulmonary tuberculosis. That in many initial cases a very careful clinical examination alone suffices will not be disputed. But in just as many cases this alone is insufficient, certainly in the material sent to the sanatoria without characteristic clinical symptoms and without medical reports. We will only mention the badly-nourished and narrow-chested men, who are medically excluded from military service, and the anæmic and chlorotic girls who largely fill our women's sanatoria. Malnutrition, chlorosis, &c., may be at the root of latent tuberculosis; but at any rate as frequently it has no connection with it. These may be all suspected of tuberculosis, but it is often left to the sanatorium to decide whether they are cases of active pulmonary disease needing treatment.

**Objection that  
Reaction gives no  
Clue to  
Site of Disease.**

The objection is raised that tuberculin diagnosis gives no certainty as to the seat of the tubercular focus in the lung and does not distinguish in adults between active and inactive disease. This is justified where one is limited to the local tests; but it neglects the fact that although *alone* the subcutaneous test does not avail much, yet in combination with other means of early diagnosis it is of the greatest assistance in the certain and early recognition of active pulmonary tuberculosis.

**The Focal  
Reaction.**

The subcutaneous tuberculin reaction in cases of pulmonary tuberculosis is generally accompanied by symptoms which show the lung to be the seat of disease. The frequent spontaneous com-



plaints of dragging, stretching, or shooting pains in the chest and increased irritation and cough are often confirmed by the appearance or increase of sputum. As early as 1890, Robert Koch described the "increased cough and sputum after the first injections" as a "local reaction" and assumed that similar changes occur in the lungs as are directly observed in lupus. To-day we can prove the occurrence of these "local" reactions in tubercular lungs (focal reactions), although their intensity does not always reach any definite point.

**Its Nature.** The focal reaction consists of the appearance or increase of physical signs: râles occur, or where these were present before become clearer or more frequent; well-marked alteration in the breath sound over the affected spot in the sense of impurity; jerkiness, roughness, or sharpness; diminished resonance becomes more marked or extends; localized pleuritic symptoms become plainer.

In consequence of the focal reaction the demonstration of tubercle bacilli may be made possible, as in the case illustrated by Chart 8. This has previously only seldom been done; with the help of the antiformin method it now succeeds more frequently.

**Demonstration of Focal Reaction.** As to the frequency of a physically demonstrable focal reaction in the lungs, exact estimates have been furnished by Kammerer [106], Otten [107], v. Romberg [108] from the Tübingen Medical Clinic, and by Walterhöfer [109] from the Wilhelmsheim Sanatoria.

Of 324 patients in the Tübingen Clinic who, between October 1904 and October 1909, received subcutaneous tuberculin on account of suspected apical changes, 197 (=60.8 per cent.) gave an apical focal reaction and also a general reaction, 24 (=7.4 per cent.) a focal reaction without simultaneous general reaction, 76 (23.5 per cent.) a general reaction only, and 27 (=8.3 per cent.) neither focal nor general reaction. In three-quarters of the cases the apical reaction took the form of the occurrence or increase of dulness; only in one quarter was it exclusively an auscultatory phenomenon. In less than half the cases was the increase of the percussion signs accompanied by fresh or increased râles or the like.

In the Wilhelmsheim Sanatoria 156 suspected cases were tested; of these 46 were proved neither tubercular nor needing treatment. Of the remaining, 110 proved to have active disease, 60 (=54.5 per cent.) gave a focal reaction, of which 55 were proved by auscultation and 5 by percussion. The auscultation signs consisted in 48 cases of crepitation râles, and in 7 of pronounced changes in the breath-sound.

It is also of interest that of the 197 cases in the Tübingen Clinic which gave neither focal nor general reaction, 118 reacted to a tuberculin dose up to 2 c.mm., 63 only to 5 c.mm., and no less than 16 required a dose of



10 c.mm. to call forth a focal reaction. This last fact is important with regard to the attitude to be adopted towards the question of the maximal test dose.

**Recognition of the Focal Reaction.** The focal reaction is usually demonstrable for two to three days; the physical signs seldom last up to four or five days. Very gentle percussion and very careful and repeated auscultation are necessary for its recognition.

The conditions here are no different from those in chest examination in general. Even sanatorium doctors do not agree as to which of the methods—percussion or auscultation—deserves recognition as the more important for diagnosis. This difference of opinion must also find expression in examining the chest for the presence or absence of a focal reaction. Therefore it is not remarkable that in the Tübingen Clinic a preponderance of percussion phenomena and in the Wilhelmsheim Sanatoria of auscultation signs has been recorded. Our own experiences coincide with those of Waltershöfer, that the proof of a focal reaction by percussion is attended with greater difficulties and that it is more frequently and certainly demonstrable by auscultation, especially by the occurrence of crepitation râles. We should like, without at present being able to give percentage figures, to impress the fact that in the majority of cases there are simultaneous subjective symptoms and objective percussion and auscultation signs which refer the site of the reaction to the apices of the lungs, the pleura, the tracheo-bronchial glands, and so on. At any rate, both methods are necessary to determine whether changes in the lung have or have not taken place in a clinically doubtful case and so to give a positive or negative diagnosis.

**Safety.** No injury to the organism has ever been noticed, nor has the condition of the lungs been made worse by the focal reaction.

v. Romberg and Olten point this out expressly, and we wish to confirm it from a still wider experience in order to meet the objection that it is dangerous to use the subcutaneous test just because of the focal reaction in the lungs.

**Advantages of Focal Reaction.** The great advantage of an apparent focal reaction is that it shows the active character of the pulmonary tubercular disease. We have, therefore, from the beginning preferred the subcutaneous tuberculin diagnosis to the local tests, and now find ample confirmation of our point of view in the above-mentioned facts published by the Tübingen Medical Clinic.

Further reports from this source, made on a average two and a half years later, showed that of eighteen individuals who showed neither a general nor a focal reaction and underwent no treatment, seventeen remained permanently healthy and fit for work, and only one two years later was taken ill with fistula of the anus and tuberculosis of the larynx.



Out of forty-seven examined later who had only given a general reaction, forty-four were found to be healthy and fit for work, although only two had taken a course of treatment at the sanatorium. Three showed a deterioration in the condition of the lungs and in the general well-being.

On the other hand, the subsequent examination of 135 individuals who had given a focal reaction gave much less favourable results, although those examined had with one exception spent a long time in a sanatorium. Two had died, eighty-two cases had to be pronounced worse, and only fifty-one were permanently fit for work and showed a favourable inactive condition of the lungs. And here it was noticed that the number of those who had improved was relatively much higher among the private patients than among the poorer sanatorium patients.

**Focal Reaction  
indicates  
Active Disease.**

The result of these subsequent investigations is very noteworthy. Above all, it points to the great difference in the course of the apical disease between those cases with focal reaction and those with general reaction, without focal symptoms. In the first category, in spite of treatment in sanatoria, nearly three-fifths were found to be in a worse condition, only two-fifths stationary and fit for work, but on the other hand those in the second category were all, with few exceptions, and without a course of treatment, in an unchanged condition. From these facts we must conclude that focal reaction in the apices definitely indicates fresh active pulmonary tuberculosis, while the general reaction only permits us to infer that there is an infection somewhere or other in the body. This enormously increases the importance of the subcutaneous tuberculin test in the early diagnosis of pulmonary tuberculosis. And it is quite an unjustifiable depreciation of the value of tuberculin diagnosis if the general reaction alone is selected from the complex of its reactive phenomena and identified with v. Pirquet's test in adults in diagnostic significance. For even this is not correct. We call to mind numerous observations when adults, clinically tubercular suspects, reacted promptly or late, slightly or severely to the cutaneous test, but who displayed no sign of general or febrile reaction to subsequent diagnostic injections. In these cases the positive cutaneous reaction signified the presence of tubercular *infection*, the negative subcutaneous test the absence of tubercular *disease*.

We must make use of it in apical changes, the etiology and activity of which is doubtful, so as to be able to note the appearance or absence of the focal reaction, and thereby select the course of treatment. Whether special treatment is indicated or not in individual cases for those patients who only give a general reaction to subcutaneous tuberculin will depend on the history, the general



condition, other clinical observations, &c. Treatment is necessary for those cases which react generally and locally when the focal reaction has been demonstrated.

**Tuberculin  
Diagnosis in  
Pregnancy.**

Tuberculin diagnosis is of special importance where suspicion of tuberculosis is present in pregnant and lying-in women. Whether treatment must be commenced during pregnancy, whether special measures must be taken for the confinement (induction of labour), whether suckling is to be allowed, are questions of such urgent importance to mother and child that the diagnosis must not only be made in good time, but with certainty. An unfavourable influence of the diagnostic injection on these patients has not been observed. Labour pains have never resulted nor has the child been harmed.

**Differential  
Diagnosis.**

The second indication for tuberculin diagnosis is the occurrence of difficulty in interpreting a disease which is certainly present. The question may arise whether tuberculosis of the lung is present, or carcinoma, or sarcoma, which may also give rise to hæmoptysis and impaired percussion, even at the apices, or whether the condition is one of infiltration due to echinococcus, or of actinomycosis, or of syphilis, which may all occur with hæmoptysis, wasting, and night-sweats. In the latter case care is necessary in the interpretation of the tuberculin reaction, as local and general reactions have been said to occur with carcinoma, syphilis, and echinococcus. This is clearly because in addition to the carcinoma or syphilis which are the chief feature in the clinical picture, tubercular foci are also present in the body. Therefore a negative result of the test is the more valuable. As an example we have given the case of a patient with unilateral dulness of the upper lobe and blood-stained purulent sputum containing no tubercle bacilli; he failed to react in any way to tuberculin and was suffering from carcinoma of the liver and metastasis in the lung. The course of the disease pointed to a malignant, the hæmoptysis to a progressive process; if this had been of a tubercular nature, a reaction would certainly have occurred to subcutaneous tuberculin doses of 1—10 c.mm. (Chart No. 11).

More frequently in the case of areas of dulness, catarrhal signs or thickenings of the pleura will it be necessary to decide between pulmonary tuberculosis and simple koniosis, bronchitis, bronchiectasis, rheumatic or traumatic pleurisy, &c. Besides these Krönig [110] has recently called attention to collapse induration of the right apex due to obstructed nasal breathing,



simulating on physical examination right apical disease, although etiologically having nothing whatever to do with tubercle. These various conditions together are not very infrequent, a fact shown by the annual reports of the sanatoria and by the observations of Blümel [111] and ourselves. But we must leave it undecided whether many of these signs are not due to a quite obsolete, shrunken and healed tubercular apical process. Tuberculin will in such cases lead to the diagnosis being made, but only when taken in conjunction with clinical methods; from the divorce of the two we cannot too strongly warn.

### Safety.

With the recognition of the special diagnostic value of the subcutaneous tuberculin test, a doubt has been expressed as to whether patients suffering from pulmonary tuberculosis may be injured by the rapid increase in the doses of tuberculin until the focal reaction takes place. Especially the question has been asked whether sometimes the general and focal reactions are not too severe and may not rouse into activity old, inactive disease of the apex of the lung. One can hardly concede even the possibility of such a thing. For truly healed apical foci will not become the site of a focal reaction and active processes in the lungs do not suffer any injury according to our many years' experience. In the very rare observations to the contrary the question whether they are *post hoc* or *propter hoc* does not seem to us to be conclusively answered. In any case, we must at least agree with Penzoldt's [105] standpoint at the Congress on Internal Medicine (1910): "With the exercise of the greatest precaution, ill-effects have been so very seldom observed in thousands of tests that they may be considered as negligible." By precaution must be understood attention to the technique, the indications and contra-indications.

### Ulrici's Criticism of the Subcutaneous Method.

Ulrici [112] has recently reported that he has performed the subcutaneous test on 120 patients, and that "amongst the 106 general reactions there were, in addition to seventeen severe febrile reactions, nine cases showing exquisite harm due to the tuberculin, although this was fortunately only temporary." The severe febrile reactions consisted of temperatures of 39° to 40° C. and over, "which is, at any rate, very unpleasant for the patient." This must be admitted, and shows that the subcutaneous test must not be performed *experimenti causa*, but is limited by definite indications and contra-indications. But when, in another part of the same speech, Ulrici states that he has given test tuberculin injections to "thirty-six patients with pulmonary tuberculosis in the first to the third stadium," and has brought about more or less severe fever, such tuberculin diagnosis is of course quite indefensible.

In addition, Ulrici has observed the following "serious results": (1)



Four weeks' duration of subfebrile temperature in two cases. (2) In one case, lytic fall of fever from  $40^{\circ}$  C. only after seven days. (3) In three cases, particularly severe malaise and serious objective condition after the injection. (4) In one patient very severe febrile intestinal catarrh which occurred simultaneously with the reaction and persisted for fourteen days. (5) A case of acute serous otitis occurring with the reaction which was treated for three weeks before a cure was effected. (6) In one patient, complete paresis of the sphincter vesicæ, which gradually disappeared in three weeks. Finally, Ulrici claims that a positive tuberculin reaction not infrequently causes a fairly severe psychical shock which may have disastrous results. The possibility of such considerable bodily and psychical damage caused by a positive reaction is considered by him one of the many reasons for the rejection of the subcutaneous test in ambulant practice.

In reply to this, we must state that during the last ten years we have made at least 10,000 to 12,000 subcutaneous injections in upwards of 4,000 tubercular suspects. In both males and females we have observed some 1,000 high febrile reactions which at their height were more or less unpleasant and troublesome, but in two, three, or at the most four days, generally gave place to a feeling of increased well-being. Presuming that the tuberculin injections for diagnosis are indicated and not given without choice or consideration, these phenomena of the specific diagnosis, even in tuberculosis of the third stadium, are such as every doctor can make himself responsible for, and will not be regarded or described by his patients as "harm." Further, amongst about 4,000 tuberculin reactions we have never observed a single one which entailed a week's fever, nor severe febrile intestinal catarrh, nor acute inflammation of the middle ear, nor any paralysis of the sphincter vesicæ. But we can record that of three patients in whom the test injection was not made for purely external reasons, there took place at the intended time of injection in one acute suppuration of the middle ear spreading to the labyrinth and subsequent chronic ill-health, in another tubercular meningitis developed, and the third was found dead in his bed on the morning following the day when the injection should have been made without the cause of death being definitely decided. We must leave it open to the judgment and common-sense of the reader whether he will accept the alarming accumulation of "exquisite harm caused by tuberculin" which Ulrici has observed in but 106 reactions, or whether he will share our opinion of the harmlessness of diagnostic injections applied *lege artis*, which is held by Penzoldt, F. Kraus, and others and is based on some thousands of personal observations.

Psychic shock with serious results caused by a positive reaction has never been observed in our daily intercourse with reacting patients, not even amongst a large number of female patients. Therefore, on this score again, we cannot advise abstention from the method, leaving the patient doubtful as to his disease or giving him a faulty diagnosis.

### Method.

What form, then, does the method of tuberculin diagnosis take in practice when tuberculosis of the lung is suspected? In the first place, the local methods of reaction, *i.e.*, the cutaneous, percutaneous, and conjunctival tests, are to be employed, and they alone in all cases where the subcutaneous method is contra-indicated; when fever



is present or hæmoptysis has recently occurred, in cases of cardiac and renal disease, of epilepsy, hysteria, and severe neurasthenia, in cases where intestinal or miliary tuberculosis is suspected, in individuals recovering from acute disease or otherwise in a feeble state of health, in all cases of severe diabetes, tendency to apoplexy, advanced arteriosclerosis and amyloid degeneration of the abdominal viscera.

#### Cutaneous Test.

In any particular case it must be borne in mind that in adults the cutaneous test—which is to be preferred to the percutaneous—is also positive in the case of foci in lung and bronchial gland so inactive as to no longer deserve the name of disease. In adults, then, a positive cutaneous reaction points only to a tubercular infection having some time occurred, whereas a negative reaction excludes with great probability the presence of tubercle in the body and hence also in the lung. We cannot confirm Kögel's [113] statement that a deferred and often slight cutaneous reaction is characteristic of fibrous tubercular processes without tubercle bacilli in the sputum; on the contrary, we have usually observed prompt and severe cutaneous reactions in this form of the disease.

#### Conjunctival Test.

The conjunctival application of tuberculin in suspected pulmonary tuberculosis is *a priori* limited to individuals with sound eyes. This greatly restricts its field of usefulness; and there is yet a further restriction. According to our comparative investigations [59], a single instillation is quite insufficient for purposes of diagnosis; the same applies also to repetition with 4 per cent. dilution in the same or the other eye. Of the early cases of pulmonary tuberculosis, just those in which the method is indicated, only every alternate case reacts to a second instillation. Tuberculosis can with certainty be excluded only after fourfold repetition on the same eye has occasioned no reaction. Hence in those persons in whom the first two instillations remain negative, the absence of pulmonary tuberculosis may not be assumed; in at least 50 per cent. of cases, this would involve an error with far-reaching consequences.

#### Fallacies of the Conjunctival Test.

We must state that the conjunctival test is highly unreliable for early diagnosis: it fails just where it is most important—in the initial stage of pulmonary tuberculosis. With advancing disease the conjunctival reaction becomes more trustworthy; in Stadium II (Turban), 75 per cent. of cases react to two instillations, in Stadium III 100 per cent. even; exception



must be made for the final stages and for cachectic patients who do not react at all. Thus the conjunctival reaction is not the reaction of initial pulmonary tuberculosis, but of the advanced open stages with bacilli in the sputum. But for pulmonary tuberculosis of Stadium II and III, tuberculin diagnosis is unnecessary. If the conjunctival reaction is positive, this justifies no conclusion as to the site of the tubercular focus in the lung, its active or inactive character or the prognosis. Wolff-Eisner's view that the conjunctival reaction is the reaction of *active* pulmonary tuberculosis seems quite incorrect.

**Insufficiency  
of the  
Local Tests.**

From all this it will be seen that in the early diagnosis of adult pulmonary tuberculosis no crucial significance can be admitted for the local reaction methods. Especially in pregnancy and confinement, their significance is influenced by processes dependent on these conditions, not on tuberculosis.

In the institution, cutaneous and conjunctival tests may be used either separately or simultaneously prior to the subcutaneous test. But their disadvantages must not be lost sight of, especially their uncertainty. If both cutaneous and conjunctival tests are positive, then tuberculosis may be decided upon without any indication of its site or character. If one or both are negative, the absence of a tubercular focus is not demonstrated. On the contrary, it must again be emphasized that both methods may fail in spite of active, even open pulmonary tuberculosis being present.

**Subcutaneous  
Test.**

In all these cases the subcutaneous method has finally to decide whether tubercular disease is present or not. If the cutaneous test is positive, but the subcutaneous negative, then it is certain that there is no active pulmonary tuberculosis and the supposition that there is an obsolete, healed, or inactive focus is justified. Such cases are constantly diagnosed by us and are not admitted for sanatorium treatment. The subcutaneous tuberculin method is therefore not so sharp and sensitive as the cutaneous reaction.

Nevertheless, the question must be raised—of great importance in general practice—whether every patient who reacts to the subcutaneous injection is suffering from active tuberculosis and therefore requires treatment. In consideration of the facts established by Franz, Kammerer, Otten, and v. Romberg, and already mentioned earlier, we must answer this question in the negative. Among those who give a reaction, a selection has to be made of those who require treatment. Only those will be looked upon as



tubercular patients requiring treatment who either, with good general condition, give a focal reaction after subcutaneous injection, or who, without any demonstrable focal reaction have an undoubtedly positive clinical history characteristic of the initial stages of pulmonary tuberculosis (cough, sputum, loss of weight, night sweats) combined with a condition of the lungs which gives rise to more or less suspicion of tuberculosis. Therefore what we have said for years and wish once more to emphasize here, still holds good: The subcutaneous tuberculin reaction by itself and apart from all clinical methods of examination, only indicates, as a rule, that tuberculosis is present, but in conjunction with clinical history, inspection, percussion, and auscultation (focal reaction), it is still to-day the supreme aid to the diagnosis of the active initial stage of pulmonary tuberculosis in adults.

**Value in  
Prognosis.**

The tuberculin reaction is also of use in the prognosis of tuberculosis. Especially in pulmonary tuberculosis the clinical methods are not reliable enough and for the most part are insufficient for the prognosis. Moreover, eleven-twelfths of all deaths from tuberculosis are the result of pulmonary tuberculosis, and only one-twelfth from other forms of tuberculosis, so that it would seem well here to discuss the question of the prognostic importance of the tuberculin reactions.

The cutaneous reaction tells us nothing as to the prognosis of patients suffering from pulmonary tuberculosis, for it only indicates that somewhen and somewhere the organism in question has been infected with tubercle bacilli. So that the cutaneous reaction of v. Pirquet is a somewhat rough method of diagnosis and by no means a help in prognosis. The suggestion, too, that a deferred cutaneous reaction is a good criterion for prognosis, and that a rapid reaction in a manifest case of tuberculosis is an unfavourable prognosis, is more a matter of speculation than fact. Only this much seems proved—when phthisical patients do not react at all to the cutaneous test the prognosis is unfavourable, and that with a more severe cutaneous reaction or one gradually becoming more severe, there is more likelihood of the disease taking a favourable course. In cases of cachectic tuberculosis the main reason for the absence of reaction is not the phthisis but the cachexia, because in cases of slight or inactive tuberculosis, which are cachectic from other causes, the cutaneous reaction does not usually take place.

What applies to the prognostic significance of the cutaneous reaction must also hold for the conjunctival. The same specific



nature of the two reactions is a proof of this: the nature of allergia is such that the allergia of the mucous membrane cannot show more than the allergia of the skin. We have proved by numerous observations [59] that no prognostic conclusions can be drawn from the degree of the conjunctival reaction and that an unfavourable significance by no means always attends its absence in manifest pulmonary tuberculosis. We agree with Heinemann [114] that it would be a mistake for the doctor to give an unfavourable prognosis in a case of manifest tuberculosis merely on the ground of a negative conjunctival test, or to allow it to influence the therapy either as regards the commencement of some definite treatment or operative measures (abortion, &c.). A method such as the conjunctival test, which is not really reliable as regards diagnosis, must be still less reliable for prognosis. For prognosis is only a more elaborate and finer diagnosis. At any rate, we cannot share the favourable view of the prognostic value of the conjunctival reaction taken by Wolff-Eisner, Meissen, Schuster, and Baer.

The subcutaneous test is of some assistance in prognosis, according to whether it produces a focal reaction or not. v. Romberg's statements [108] may be quoted in this respect. On the other hand, no prognostic conclusions whatever can be drawn from the size of the tuberculin dose, the height of the fever or the curve of reaction.

## 2.—TUBERCULIN DIAGNOSIS IN TUBERCULOSIS OF THE RESPIRATORY TRACT.

### Nasal Tuberculosis.

Tuberculosis of the nose is usually secondary and does not usually present any diagnostic difficulty, especially when its etiology is indicated by the primary disease. The solitary abscess on the front cartilaginous part of the septum shows, after removal of the crust, a characteristic appearance. A tuberculoma can hardly be confused with a malignant growth. And in lupus, which, as a rule, commences high in the front angle of the vestibule, nodules spread through the nostrils to the outer surface of the nose; in the later stage it is characteristic of lupus infiltration that on the raised tuberculated surface, in addition to irregular ulceration, there are necrotic changes.

### Diagnosis.

There are difficulties in differential diagnosis when eczema at the nostril hides the process, also between tubercular and gummy abscesses and in those tubercular and syphilitic processes which bring about thickening



and destruction of the septum and may even extend to the osseous portions of the nose. If in the base of an ulcer or in a piece of excised tissue no tubercle bacilli or spirochaetes are found, and test treatment with potassium iodide does not lead to diagnosis, then tuberculin must be used. As a rule, local application will suffice. We recommend the employment of the nasal reaction with old tuberculin described on p. 69. If doubt still exists, the subcutaneous test may be applied with very careful observation of any focal reaction. At any rate, where tubercle of the nose is suspected, diagnosis must under no circumstances be abandoned half-way. The practitioner must do more than hitherto; only in this way will the deplorable number of victims be reduced who owe their condition to a tardy recognition of nasal lupus.

In tuberculosis of the naso-pharyngeal space and trachea, the diagnostic conditions are similar to those in tuberculosis of the oral cavity, pharynx and larynx; the following is a short summary:—

**Laryngeal  
Tuberculosis  
Indications.**

Primary and solitary laryngeal tuberculosis, that is cases in which the tubercular disease of the larynx is the first and sole localization of the tubercular process, are very rare phenomena. Laryngeal tuberculosis occurs, as a rule, as a complication of pulmonary. If the latter has passed the initial stage and is recognizable by physical and bacteriological examination, the diagnosis of a simultaneous laryngeal affection will generally afford no difficulty. The case is different when it is a question of slight changes in the lung of which the etiology is not clear, and where the laryngeal symptoms are more subjective than objective. In such cases the patient may complain of the voice becoming readily tired, of some thickness of speech in the early morning or after keeping silence for some time, of indefinite feeling of pressure or tendency to cough, especially on change of temperature; but examination with the mirror reveals either nothing pathological or not enough to confirm a suspicion of specific changes. Acute and chronic catarrh in tubercular patients, causing redness and swelling in the larynx, may simulate laryngeal tuberculosis; the same may be said of epithelial necrosis of the vocal cords, so-called catarrhal abscesses, erosions and sore places in pachydermy of the processus vocalis and swelling and folding of the mucous membrane of the posterior wall of the larynx.

In all such cases the frequency of tuberculosis over all other laryngeal affections forces one to ask the question whether



tuberculosis is not present. And the question put must be answered with the help of tuberculin diagnosis, as the same applies for laryngeal as for pulmonary tuberculosis in respect of healing: the earliest stage is the most curable.

**Diagnosis  
usually made  
too late.**

It is shown by experience that the cases of laryngeal tuberculosis coming up for sanatorium treatment are in a large percentage further advanced than those of pulmonary disease. This is the more striking, since the diagnosis of commencing laryngeal disease is the easier, the explanation doubtless being that the practitioner in general examines the larynx too little and too late, and often for the first time when severe pain on swallowing or permanent hoarseness is complained of. It should hence be made a rule to examine the larynx where pulmonary disease is suspected and *vice versa*, and to observe the result of the tuberculin injection both on lung and on larynx, since for the latter the question is so easily and certainly decided.

To establish the diagnosis, tuberculin may be necessary in the presence of ulceration of the larynx, which the clinical history, constitution, and signs leave doubtful whether of parasitic, of syphilitic or of malignant nature.

In the case of new growths—fibroma, papilloma, carcinoma—microscopic examination of a piece of excised tissue will lead certainly to the diagnosis. But for the practitioner the technique is usually impracticable. If syphilis is suspected, a therapeutic injection of salvarsan or large doses of potassium iodide may produce a healing tendency and disclose the etiology; but there are many cases in which salvarsan cannot be used, an anti-syphilitic cure postpones the diagnosis too long or does not give a definite result (*e.g.*, in the not infrequent mixed forms of syphilis and tuberculosis). Hence in these cases it is well, as Neisser [115] proposes, never to leave the diagnostic tuberculin injection untried.

**Choice of  
Method.**

In regard to the choice of the diagnostic method, the same considerations in general apply as for pulmonary disease. But the superiority of the subcutaneous method deserves still greater emphasis in laryngeal tuberculosis. For the observation of the focal reaction, making the diagnosis a matter of certainty, the conditions are much more favourable than in the lung.

**Signs of  
Reaction.**

The signs of the focal reaction in the larynx are also those of inflammation; in the case of closed foci, of inflammatory



swelling and redness; in open ones, of superficial necrosis. The reactive processes can be so exactly followed with the mirror that laryngeal tuberculosis may be excluded when the picture remains the same before, during, and after the injection. Generally in the course of the reaction fleeting pains occur or become more noticeable, or at any rate a "curious feeling as if something were in the larynx" is noted.

The voice also, where the focus lies in the parts concerned with its production, becomes less clear. On the other hand, even in cases of advanced disease, swelling resulting in obstruction of the lumen, with stridor and difficulty of breathing, does not occur, a fact specially emphasized by B. Fränkel [116]. But for these cases, as has been said before, there is no question of employing the method at all. Softening of the process in connection with a focal reaction *may* occur, but only in those tubercular changes of the larynx which are destined to break down even without reactive inflammation and must soften and be cast off to bring about a cure. Therefore there is no reason why the subcutaneous test should be rejected or postponed, or less certain diagnostic methods, impracticable for the practitioner, be recommended. Spreading of laryngeal tuberculosis after diagnostic injections has never been observed. The dangers are theoretical and warnings against the use of tuberculin for early or differential diagnosis on the ground of focal reactions are unjustified.

### 3.—TUBERCULIN DIAGNOSIS IN TUBERCULOSIS OF THE DIGESTIVE ORGANS.

**Mouth.** In the oral cavity, tuberculosis is chiefly localized in the tongue, cheeks, lips, palate, mucous membrane of the gums, and in the tonsils. In addition to the ulcer form, there occurs the tuberos form and lupus infiltration. All three forms often present a certain amount of difficulty in differential diagnosis, especially in distinguishing from cancer and syphilis. If careful inquiries, appearance, histological and bacteriological examination of the secretion from the ulcer or piece of excised tissue and a therapeutic course of potassium iodide or salvarsan all fail to give a clue, then tuberculin diagnosis may be used with advantage. Of the various methods, the subcutaneous is the best, as it brings about characteristic focal reactions in tubercular processes in the mouth which are easily recognized in visible situations.



**Pharynx.** The same applies to tuberculosis of the pharynx, which is observed in miliary form, as diffused infiltration and as lupus. Here again, owing to the great possibility of mistaking tubercular changes for syphilitic, test tuberculin injections are often indispensable and afford the desired clue.

**Œsophagus and Stomach.** In the diagnosis of the very uncommon tuberculosis of œsophagus and stomach, we have found that tuberculin is of no use. Petruschky and E. Fischer recommend the subcutaneous method where tuberculosis of the stomach is suspected, as it may produce indubitable focal reactions. As such Fischer has observed increase of spontaneous pain on pressure and nausea. But we must offer this warning: In individuals with completely sound stomachs and lungs, a tuberculin reaction may produce sudden gastric symptoms with nausea and increased pain on pressure, in the tracheo-bronchial glands by irritation of the vagus. This is easily explained by the anatomical situation of vagus and hilus glands, by the frequent tubercular infection of the latter, and by the significance of the vagus as a motor, vascular, reflex and sensory nerve for the stomach; and this is certainly much more often the cause of a reaction than a tubercular gastric ulcer.

**Intestines.** Owing to the almost exclusively secondary character of intestinal tuberculosis in adults, tuberculin diagnosis can have no practical value; even from the subcutaneous test no topical diagnosis can be expected. Only where a tubercular primary affection is not capable of clinical proof or its tubercular nature not settled beyond doubt, can specific diagnosis explain the state of affairs to a certain degree. This will be the case chiefly in primary intestinal and mesenteric glandular tuberculosis of childhood and youth.

As for the differential diagnosis of ileo-cæcal tuberculosis and chronic appendicitis or carcinoma, which is of great difficulty and practical importance, tuberculin diagnosis can scarcely be considered; the local tests are not likely to succeed and the subcutaneous method is usually contra-indicated. The production of a focal reaction is specially to be avoided when the constant painfulness of circumscribed areas of the abdomen point to the presence of circumscribed peritonitis as a result of deep ulceration of the intestine.

Fistulæ around and about the rectum and anus, and rectal ulcers, secrete more freely after tuberculin injections when they are of a tubercular nature.



#### 4.—TUBERCULIN DIAGNOSIS IN UROGENITAL TUBERCULOSIS.

Tuberculin is being used in the diagnosis of tuberculosis of the bladder and kidneys and in urogenital tuberculosis, although urologists and gynaecologists are not agreed in all points.

##### Cutaneous Test.

Of the local tuberculin tests, an attempt was first made to use the cutaneous inoculation. Thus Hohlweg [131], in the Giessen Clinic, observed twelve positive reactions to 25 per cent. old tuberculin in thirteen cases of tuberculosis of the urinary passages, but could not draw any conclusions as to the presence of tuberculosis of the urinary apparatus itself. Veit, Kraus, and Kaminer have given emphatic warnings against gynaecological operations dependent upon the result of cutaneous inoculation. The interruption of pregnancy, too, because of positive cutaneous reaction, is not allowable, especially as R. Stern's [132] systematic experiments have shown that the practical utility of the cutaneous test is considerably reduced during the second half of pregnancy.

##### Conjunctival Test.

The conjunctival tuberculin test has been employed in urology with unequal success. According to Necker and Paschkis [133], who use the tuberculin of the Pasteur Institute, a positive conjunctival reaction is of assistance in urology, especially in distinguishing suspicious cases. Casper [134] and Karo [135], on the contrary, both report most striking errors in diagnosis: it was negative in a number of cases in which operations revealed tuberculosis of the urinary passages and, on the other hand, the reaction was positive without the diagnosis of tuberculosis of the kidneys being confirmed by the operation. Hohlweg [131], in seventeen cases of definite tuberculosis of the urinary passages, only found four distinct and two feebly positive conjunctival reactions, eleven being negative. Similarly Hörrmann [136] found the test of little use in one of the Munich gynaecological clinics; in no case did the conjunctival test definitely decide the tubercular or non-tubercular nature of genital complaints. Stern also states that pregnancy in itself influences the diagnostic value of the test.

Further experiences need not be demanded after the proceedings of the Fourteenth German Congress for Gynaecology (1911). The operations in question are usually radical and indications for operative measures cannot be drawn from a quite uncertain diagnostic method.

##### Value of Subcutaneous Test.

The subcutaneous tuberculin test gives rise in a large percentage of cases to focal reactions, increase in susceptibility and subjective symptoms, which may be of the



utmost value in the diagnosis of tubercular disease of the uropoietic and genital apparatus.

**The Focal Reaction  
in Tuberculosis  
of Bladder;**

In vesical tuberculosis the focal reaction consists of frequent micturition of an urgent character and of pain in the region of the bladder.

**in Tuberculosis  
of Kidneys;**

In tuberculosis of the kidneys, painfulness in the region of these organs gives a clue to the site of the disease; but our observa-

tions, with those of Pankow, show that uni- or bilateral painfulness in a focal reaction does not definitely decide whether one or both kidneys are affected. Besides pain in the kidneys, other phenomena come into consideration as focal reactions: Difficult micturition, hæmorrhage, passing of shreds and dragging pain in the ureter (Hock, Karo, Brückner, Hohlweg). The latter, by limiting his maximum diagnostic dose to 1 c.mm. of old tuberculin, has observed only a focal reaction; this dose is clearly too small even for the diagnosis of tuberculosis of the kidneys. We must agree with Hohlweg that cystoscopy and catheterizing of the ureters in combination with a search for bacilli is the most reliable method for the diagnosis of tuberculosis of the kidney; but search for bacilli in the majority of initial cases is by no means the quickest method, and cystoscopy and catheterizing of the ureters are often enough unsuccessful even in skilled hands. Thus Brücker has lately published a case of a patient, aged 12, in whom the consultant physician excluded cystoscopy as technically impracticable and was unable to answer the question of which kidney was diseased. In this difficult situation, which occurred in spite of modern urological methods applicable to children, a topical diagnosis was made by means of the subcutaneous test and the diseased kidney removed by operation.

**of the Testis and  
Epididymis;**

In tuberculosis of the testis and epididymis there follows on the injection a sense of dragging in the cord, tenderness, pain, swelling, or even abscess formation at the site of the affection.

**of the Vagina  
and Vulva;**

In vaginal and vulvar tuberculosis the symptoms of reaction are visible and of use in diagnosis.

**of the  
Urogenital  
Organs;**

In urogenital tuberculosis, also, when not too old and not yet begun to heal, a focal reaction generally occurs, which varies according to the site of the tubercular affection. Birnbaum [137] observed focal reactions in 94 per cent. of cases of urogenital tuberculosis in women; he therefore



considers the diagnostic tuberculin injection to be "an aid at some times indispensable and of primary importance in the diagnosis," and that it deserves wider recognition.

of the  
**Female Genital  
Organs.**

In tuberculosis of the female genital organs the reaction produces severe abdominal pain, with bearing down and a feeling of weight in the pelvis. When the uterus is the seat, pain is present in the hypogastrium and sacral region, sometimes also bleeding; digital examination will then generally make it easier to decide whether the reaction is taking place in the uterus or appendages. Prochownick [138] obtained the best diagnostic results in genital tuberculosis in women by using the subcutaneous method, so that he has remained faithful to it ever since the discovery of tuberculin. Krönig, too, states "only subcutaneous old tuberculin injections have a diagnostic significance"; but he adds that for clinical use they have the disadvantage of a result deferred often by ten to fourteen days and of disturbing the general well-being by the general reaction. The opposite view is taken by Schlimpert and Zoeppritz [139], who, in the German Gynæcological Society at Munich, in 1911, rejected all the tuberculin tests, including the subcutaneous, as unreliable. v. Franqué [140] also considers it "not quite reliable" in gynæcology; he states that the focal reaction is often negative, or focal and general reaction takes place without any trace of tuberculosis being subsequently found in the sexual organs, especially in hæmatoma of the ovary. Neu states that he has repeatedly observed rapid deterioration of the condition even after a cutaneous test, while Birnbaum, on the ground of his observations on gynæcological cases of tuberculosis in the Göttingen Clinic, continues to affirm that he has never observed spreading of the disease to other organs or an aggravation of the tubercular process as a result of the injection.

## 5.—TUBERCULIN DIAGNOSIS IN TUBERCULOSIS OF THE SEROUS MEMBRANES.

Of tuberculosis of the serous membranes, those of the meninges, pleura, and peritoneum must be mentioned on account of their relative frequency.

**Contra-indication  
when Tubercular  
Meningitis is  
Suspected;**

It has already been mentioned that on suspicion of tubercular meningitis, the subcutaneous method is contra-indicated because of the risk of shortening life. In children the alternative of the cutaneous test



is offered, in adults either of this or the conjunctival. It is true that both have the disadvantages of being often negative in cases of meningitis, and the failure of the reaction to appear does not therefore exclude tubercular meningitis. Therefore Engel [71] recommends the intracutaneous test which, he states, does not fail in tubercular meningitis of children. In adults also the positive reaction is of no indisputable significance.

**in Cases of Pleurisy ;** In pleurisy with exudation, the subcutaneous tuberculin test for diagnosis is also contra-indicated. Even after the acute symptoms, fever, exudation, &c., have passed away, the question of practical moment—was the pleurisy of tubercular origin?—will not always be clearly answered, because when exudate or great thickening of the pleura is present the reaction will hardly be evident, or if it occurs may be due to some other focus having no connection whatever with the pleurisy.

On the other hand, in cases of dry pleurisy a conclusion as to its tubercular nature may be drawn from the general reaction with increased pain in the side and increased or more distinct friction sounds, and the plan of treatment adopted in good time. Local tuberculin tests may be specially useful in diseases of the pleura when the subcutaneous method is contra-indicated on account of unstable or raised temperature. Employed with the necessary discrimination, they will contribute in throwing light on the etiological side of the question.

**in Peritoneal Tuberculosis.** The tuberculin injection has high diagnostic value in those cases of peritoneal tuberculosis, in which, after exclusion of disease of the heart, liver, or kidney, the diagnosis rests between carcinoma and tubercle. Here, by the occurrence or absence of the tuberculin reaction, the nature of the affection may be cleared up earlier than is possible by any other method.

The same applies when there is doubt as to whether a dry form of peritoneal tuberculosis is present, or a chronic, non-tubercular form of peritonitis. In peritoneal tuberculosis the focal reaction is characterized by abdominal pain, feeling of increased tension, flatulence, vomiting, and frequently more or less profuse diarrhoea. In all these cases, therefore, the conjunctival and cutaneous methods are less valuable than the subcutaneous test; but it must be used with caution when adhesion in the intestines is suspected. Its diagnostic reliability is vouched for by the statistics of Heimann [141], according to which in the Breslau Clinic, during the course of ten years (1898-1908), in each of thirty-six cases peritoneal tuberculosis was discovered by the



tuberculin test, and confirmed by microscopical examination of excised portions of the peritoneum. In these cases also the focal reaction was characterized by profuse diarrhoea and abdominal pain.

## 6.—TUBERCULIN DIAGNOSIS IN OPHTHALMIC TUBERCULOSIS.

In ophthalmic practice the position as regards tuberculin diagnosis has not been materially altered by the introduction of the methods of local reaction.

**Cutaneous Test.** The cutaneous reaction has been little used in ophthalmic diagnosis; no more is to be expected from it in ophthalmic than in other forms of adult tuberculosis, *i.e.*, a certain importance can only be attached to a negative result.

**Conjunctival Test.** The conjunctival reaction has found extensive application in ophthalmic practice, especially to decide the question whether an affection of the eye is tubercular or not, but certainly has not proved a blessing to the patient.

**Dangers.** Without giving details from the extensive literature on the subject, we must take the view adopted by ophthalmic surgeons (Adam, Brons, Collin, Siegrist, Stuelp, Waldstein, Stargardt, Löhlein, Rupprecht) that conjunctival reactions should never be resorted to when ophthalmic tuberculosis is suspected. And this first because of the frequent unpleasant and serious consequences following instillations in diseased eyes, and also because nothing is gained for the diagnosis of ophthalmic disease by a positive reaction; it may be caused by a tubercular focus anywhere in the body. This also holds good when the instillation is made in a healthy eye with positive results. Therefore the conjunctival reaction is of no value in ophthalmic practice. Thus the ophthalmist will, as Stargardt [117] says, take special care not to employ a method which may aggravate the condition of a diseased eye or harm a healthy one by a severe, protracted reaction. And other physicians, too, will join in refusing to "employ an organ of such dignity as the eye for this diagnostic method" (Sahli).

Wolff-Eisner [84], it is true, thinks that danger to the eye may be avoided by commencing the instillation with the weakest dilution of tuberculin 1:100,000, and slowly increasing the strength. But it rests with him to prove that such dilutions are on the one hand harmless, and on the other effective and reliable.



**Subcutaneous Test Preferable.** The subcutaneous tuberculin test, introduced into the treatment of ophthalmic diseases by v. Hippel [118], is recommended by Haab, Pflüger, Enslin, Stock, Jung, Igersheimer, Leber, Davids, Brückner, Reuchlin and others, and has lately been described by C. Hess [119] as the "most serviceable diagnostic aid." In face of the generally recognized fact that tuberculosis and syphilis are the most important etiological factors in chronic inflammation of the iris, ciliary body and choroid, it is indispensable to every oculist. For in no affection of the uveal tract can a tubercular etiology be excluded by clinical means alone, and further, in diseases of the cornea and sclerotic which do not clinically suggest tuberculosis, doubts must exist whether a tubercular infection is present. At any rate, eye specialists "without diagnostic injections can judge the etiology of many, very many cases, only by means of accessory phenomena" (Heine [120]).

**Freedom from Danger.** Diagnostic tuberculin injections in ophthalmic diseases are not only necessary but also harmless. Heine [120] on the ground of many years' observation of numerous cases in the Kiel University Ophthalmic Clinic states: "Of the many hundreds of our own diagnostic injections and the thousands recorded in the literature of the subject, there is no report of any bad results. On the contrary, the common report of all workers in this branch of medicine is that it has never done harm." Igersheimer [122] states that the local hyperæmia even frequently gives a direct impulse to absorption, and thereby to healing of the tubercular process. Heine considers the "receding reaction" in an equally favourable light; this focal reaction often occurs in connection with a positive subcutaneous test; the eye reddens, but afterwards becomes less coloured than before the injection.

**Value of Focal Reaction.** The most valuable diagnostic conclusions, both of a general kind and for the individual case, can be drawn from the subcutaneous method with consequent focal reaction. This has lately been specially emphasized by C. Hess, Löhlein, F. Schoeler, Augstein and Igersheimer, the last three pointing out the absence of any injurious effect in connection with local reaction in the diseased eye. Views only differ with regard to the frequency of the focal reaction. Whilst Augstein [121] states that a more or less distinct focal reaction in the front section of the bulb with tubercular adults is the general rule, Heine, Stock and others hold that this focal reaction, so valuable in diagnosis, occurring in the diseased eye without general reaction, is by no means common.



Therefore they consider the absence of focal reaction in ophthalmic diseases does not exclude a tubercular etiology.

**Dosage.** For the dosage Davids [123] recommends the method of the Göttingen University Clinic for Diseases of the Eye, which gives quite certain results: for the first injection 1 c.mm. old tuberculin, for the second 2 c.mm. or 3 c.mm., and for the third 5 c.mm.; more than 5 c.mm. should not be given, as other oculists also agree. F. Schoeler [124] is even satisfied with a maximal dose of about 2.5 c.mm. old tuberculin, which he reaches in very gradually increasing doses at the seventh diagnostic injection.

Augstein is still more cautious in dosage. In suspected tuberculosis of the iris he begins with an injection of .01 c.mm., and after each injection searches for focal reaction with the corneal microscope. In the Tübingen Ophthalmic Clinic, too, fractions of a cubic millimetre are used for most of the cases. Fleischer increases up to 10 c.mm. when it is a case of excluding tuberculosis with absolute certainty. Heine, also, considers the old recommendations of Koch for dosage in ophthalmic affections quite unjustifiable; only the experience that quite small quantities of tuberculin sufficiently explain the etiology induces him to begin with .1 c.mm. in adults, in children and weakly patients with .01 c.mm., afterwards doubling the dose each time until a rise of temperature occurs, as small as possible but definite. v. Michel does not employ the method for purely diagnostic purposes, but prefers to begin with the smaller doses on a therapeutic course, when, of course, the diagnosis is often made clear.

But whatever the dosage may be, great attention must be paid to the intensity and duration of the focal reaction in the eye. Therefore it must be remembered: (1) That indication for the subcutaneous test is limited to those ophthalmic diseases which are clinically doubtful or present special difficulties in differential diagnosis; and (2) that on account of the difficulty of recognizing a focal reaction in the eye, the physician should, in all such cases, examine the often slight changes of the local reaction with the ophthalmoscope, observing their nature and course.

## 7.—TUBERCULIN DIAGNOSIS IN AURAL TUBERCULOSIS.

In spite of the varying etiology of acute and chronic inflammation and discharge from the middle and internal ear, and the mastoid process, tuberculin has not made much headway as a diagnostic agent in aural practice.

Certainly doubts do not often arise, because the diagnosis of



tuberculosis of the ear can usually be made from the local and general condition and proofs of an underlying tubercular condition are also fairly frequently given in the first stage by the presence of tubercle bacilli in the secretion.

**Subcutaneous Test.** Owing to the first observations, the subcutaneous tuberculin test is considered uncertain and dangerous in aural diagnosis, although it is recommended by Schwartz, Lucae, Bezold, Schwabach and Ferreri when the diagnosis is doubtful. We also should consider a focal reaction in the internal ear hazardous.

**Conjunctival Test.** No experience is yet forthcoming of the value of the conjunctival reaction in tuberculosis of the ear. In this respect not much more is to be expected than what we can ourselves state, namely that the negative result of the conjunctival instillation does not prove with any certainty the non-tubercular character of the aural disease. But if the reaction is positive, then it is left to the observation of the physician to decide whether the tubercular focus is in the ear or elsewhere in the body.

**Cutaneous Test.** The conditions are more favourable to cutaneous inoculation, because in early childhood this gives more definite results for the aurist. Thus Schüller [125], from observations in the University Clinic for Aural Diseases in Heidelberg, comes to the conclusion that the cutaneous test in aural disease, especially in children, is the more frequently to be recommended. The diagnostic value of the negative reaction is greater than that of the positive, since the latter can only make a diagnosis of tuberculosis of the ear certain in combination with clinical reasons for suspicion.

## 8.—TUBERCULIN DIAGNOSIS IN TUBERCULOSIS OF THE SKIN.

The polymorphism of tubercular skin affections explains the differences of opinion with regard to the pathogenesis of many of them; here we will only mention the so-called tuberculides. Other inflammatory conditions of the skin often cannot be etiologicaly differentiated on the basis of clinical symptoms alone.

**Cutaneous Test:** Up to the present the cutaneous test and its Advantages and Behaviour. the inunction of tuberculin ointment have been employed and there is not the slightest reason for including the conjunctival test. Moreover, the conjunctival test in cases of lupus of the skin is generally negative, and in lupus of the face, spreading to the lids or conjunctiva, directly contra-indicated. Of the intracutaneous



method there is still no record; we imagine, however, that the intracutaneous test performed in the neighbourhood of a suspected focus would be of value owing to the subsequent focal reaction.

From the results of cutaneous inoculation in tubercular skin diseases and in those in which the presence of tuberculosis is suspected, Bandler, Kreibich, Doganoff, Moro, Oppenheim, Pfaundler and others agree that a great difference of degree in the severity of the cutaneous reaction exists between cases of cutaneous and those of internal tuberculosis. Whilst in patients with internal tuberculosis and healthy skin only an ordinary wheal-infiltration occurs, in patients with lupus, large circumscribed nodules and lichenoid eruptions make their appearance. The difference is generally readily noted. It is based on a specific hypersusceptibility of the skin to tuberculin, which also explains why specially rapid and severe cutaneous reactions are to be expected in tuberculosis of the skin.

Only in quite small lupus foci in the initial stage does the cutaneous reaction in the healthy tissue often fail. In such cases it is advisable to perform the test on the diseased tissue. If the focus is tubercular, a severe reaction then ensues after eighteen to twenty-four hours, consisting of redness and exudation with subsequent induration or transition into necrosis (Nagelschmidt). By this method even the smallest foci can be discovered with certainty.

**Indication for Subcutaneous Test.** In still more certain and characteristic manner does the subcutaneous tuberculin test act on local tuberculosis of skin or mucous membrane, especially in the case of quite small and badly marked primary eruptions, which awaken the suspicion of lupus and lichen scrofulosorum. Even in quite the earliest cases tuberculin leads to such characteristic local changes that there can no longer be doubt of the diagnosis of lupus. Even latent lichen nodules in the skin may be rendered visible.

**Focal Reaction.** The focal reaction even to small doses is usually severe, and commences four to six hours after the injection, not infrequently some hours previous to the general reaction (see Chart 12); only when the bacilli are enclosed in cicatrized tissue, in necrosis and quite recent tubercles, the focal reaction may be absent.

**Symptoms of Focal Reaction.** The most striking and earliest to appear of the symptoms of focal reaction are hyperæmia and swelling. In the case of densely infiltrated lupus the swelling is marked by its diffuse and uniform character, from which the lupus nodules stand out, red or



brownish-red. Soft lupoid tissue shows swelling and protrusion of the flat areas, and, where ulceration is present, as a rule, increased secretion. Frequently the solitary nodules which share in the reaction are surrounded by a whitish areola, and this again by a broad vivid red band, an observation first made by Koch. After the fever has dropped, swelling and redness die away and necrotic processes take the field: lupus nodules, prominent before, sink in; existing ulceration becomes deeper; granulations become necrotic and drop off, in extreme cases first turning black. Anyone who has seen a case of lupus reacting to tuberculin, subcutaneously injected, will never again have any doubt as to the specific action of tuberculin on tubercular tissue. In however distant a part of the body the injection may be made, the process is concentrated in and limited to the lupus nodule.

**Preference given  
to Subcutaneous  
Test.**

Such observations justify the preference being given to the subcutaneous use of tuberculin in dermatology over the local tuberculin test, as is also done by A. Neisser [125]. Neisser has clearly demonstrated that the cutaneous reaction may certainly prove the presence of some tubercular focus or other in the body, but not the tubercular character of a definite cutaneous affection not clinically characteristic; whereas the local focal reaction following a subcutaneous injection of tuberculin definitely testifies to the tubercular nature of the diseased focus.

Heuck [126] considers the special advantage of tuberculin injections for the diagnosis of lupus and tubercular skin diseases to be that from the extent of the local zone of reaction one can deduce the real "microscopic" extent of the process. The whole clearly defined zone of reaction round the visible focus of disease is to be considered as infected with tubercle. That is important both for the decision of the question whether a definite cure can be achieved or not and for the treatment, in order by operation to remove all the diseased part and to make sure that there shall be no relapse.

**Urgency of  
Diagnosis  
in Skin Cases.**

Since cosmetic grounds are urgent on account of the favourite localization of lupus, treatment must not be delayed until such irreparable destruction has occurred that the diagnosis is no longer doubtful to the patient or his relatives. The practitioner is guilty of a serious neglect in regard to his patient, if, on the slightest suspicion of lupus, he does not make sure of the diagnosis in order to begin the line of treatment chosen. Early and certain recognition of lupus is served by the cutaneous test or still more perfectly by the diagnostic injection of tuberculin.



## 9.—TUBERCULIN DIAGNOSIS IN TUBERCULOSIS OF THE GLANDS, BONES, AND JOINTS.

**Cutaneous Test.** Numerous observations testify to an increased cutaneous reactivity of cases of surgical tuberculosis. But in employing the cutaneous test, Wilms' [127] experiences must be borne in mind that it may prove negative in cases of fungoid tuberculosis in whatever situation, and also in patients who have not yet become cachectic. In general it is just the relatively favourable form of surgical tuberculosis, particularly of the cervical glands and soft tissues, which is characterized by very considerable reactions. According to observations in the Heidelberg Clinic, it shows a form of reaction, rare and unusually severe in pulmonary tuberculosis, which is a favourable prognostic sign of the energy exerted by the organism against the infection, and indicates a healing tendency. Weak reactions or failure to react at all in surgical tuberculosis in the initial stage or in advanced cases are of unfavourable prognosis, while decreasing reaction on repetition indicates progression of the disease and an approaching fatal issue, increasing reaction a favourable healing tendency (Hollensen).

The cutaneous reaction in surgical tuberculosis presents the same phenomena whether the tuberculin is of human or bovine origin; Detre's modification (*cf.* p. 48) has no special significance.

**Conjunctival Test.** The conjunctival reaction has also been recommended for surgical cases. According to Zoeppritz [128] it is always positive in all cases of closed tuberculosis of bones, joints, and glands without complications, whereas in closed diseases of the bones, joints and glands without any other proof of tuberculosis a negative reaction denotes with certainty the absence of tuberculosis; only in cases of fistula and open surgical tuberculosis was the reaction less reliable. These observations deserve consideration, but only after further confirmation, for especially for surgical purposes when the reaction is positive, in order to avoid faulty diagnostic and prognostic conclusions, one must always remember that the patient only needs to have quite an insignificant and clinically unrecognizable tubercular focus (*e.g.*, in the tracheo-bronchial glands) to react both quickly and severely.

**Subcutaneous Test.** The subcutaneous tuberculin test often indicates also in surgical tuberculosis the site of the disease by a simultaneous focal reaction. In tubercular glands inflammatory swelling may generally be observed after the first injection of tuberculin, accompanied by definite enlargement.



Many patients first have their attention called to the fact that they have palpable glands by the pain which occurs in them. We have also observed this after a positive intracutaneous reaction; after it has been performed on the forearm, swelling and painfulness has occurred in the axilla.

Even the subcutaneous test fails to differentiate glandular tuberculosis from true lymphatic leucocythæmia; both in tubercular and leukæmic glands reaction occurs. Thus Hegeler observed a huge swelling of leukæmic glands to 2 c.mm. tuberculin. The same holds for glandular tumours in Hodgkin's disease, which react just like tubercular; here it is evidently a case of a group reaction.

**In Tuberculosis  
of**

In the case of bone and joint tuberculosis, swelling and increased tenderness are unmistakable signs of a specific reaction.

**Bones and Joints.**

With superficially situated processes, more or less definite reddening generally occurs as a consequence of the inflammatory hyperæmia. According to Waldström [129], the early diagnosis of synovial coxitis can only be made by means of subcutaneous tuberculin injections; and, indeed, the appearance or non-appearance of synovial symptoms decides the question whether a tubercular process of the bone is isolated or already complicated with synovitis. Tubercular fistulæ secrete more actively after tuberculin injection, and by casting off undermined pieces of skin may become superficial ulcers.

No further reasons need be given for recommending the application of the subcutaneous tuberculin diagnosis for the purpose of differential diagnosis in such local symptoms, perceptible to sight and touch. On the other hand positive reactions have often not been confirmed in cases of surgical disease where tuberculosis is suspected, so that the negative result of the tuberculin test seems more important. They also appear to be not entirely free from danger. Penzoldt [105] observed in vertebral caries an immediate and lasting change for the worse. Wolfsohn [130] reports that coxitis scars which had been closed and absolutely without reaction for twenty-two years, responded to the inoculation of a small quantity of tuberculin with a typical specific reaction, burst and produced purulent abscesses with caseous crumbling contents. Tubercular abscesses of the breast present at the same time were, however, very favourably affected by tuberculin, and were healed. The burst coxitis scars also healed. This case is much quoted. We will leave it undecided whether it is an advantage or a disadvantage that tuberculosis should be disclosed by means of tuberculin, and so made amenable to treat-



ment, or that active processes, which may at any moment flood the whole organism with tubercle bacilli, should remain concealed. But it does not seem to us to show the true spirit of criticism to condemn the subcutaneous tuberculin diagnosis because of a single case which, moreover, took a favourable course in the end. Its application should be limited as far as possible, and in every case suspected of bone or joint tuberculosis Röntgen-ray examination should precede it. But when this and clinical observation do not explain the state of affairs, then tuberculin may and should be injected, presuming that marasmus, fever, or considerable pain do not contra-indicate it.

#### 10.—TUBERCULIN DIAGNOSIS IN CHILDREN'S DISEASES.

##### Necessity for Early Diagnosis.

The tendency of the present day to commence the fight against tuberculosis in the years of childhood is doubtless correct. But if success is to be obtained in tuberculosis of children, we must not wait until the foci have long been manifest or the third stage—pulmonary tuberculosis with cavities—has occurred. A *laissez aller* of the tubercular infection in childhood is still very prevalent. Whilst the strong movement for the protection of infant life has reduced the mortality from tuberculosis during the first two years of life, that of school-going children has not decreased materially during the last decade. This will surely be altered when in every tubercular focus in the child's body we recognize a danger. And occult tubercular glands or pulmonary foci are a source of serious harm to the organism. It is specially in childhood that the possibility is increased of a quiescent infection becoming extended by an injury or irritation of some kind, and this the more rapidly and generally the younger and less capable of resistance the children are. Therefore the early diagnosis of infantile tuberculosis, including the occult forms, is of imperative necessity. For this purpose we need tuberculin.

##### Frequency of Tuberculosis in Children.

The importance of the tuberculin test varies according to the age of the child, whether it is a question of sucklings, young, or older children. This may be seen from the results of Hamburger's [142] investigations, which show that the frequency of tuberculosis in children increases proportionately to advancing age; in the earliest years of childhood tuberculosis is, as a rule, active and fatal, and only with increasing years does the frequency of inactive forms of tuberculosis increase. From



*post-mortem* results, the increase of tuberculosis from 15 to 70 per cent. during the first ten years of life has been demonstrated.

**Agreement of  
Cutaneous Test  
with Post-  
mortem Results;**

With these observations the results of the cutaneous tuberculin test are in striking agreement.

New-born children without exception give no reaction, even when the mothers react positively. Bondy made the cutaneous test on 350 new-born children between the second and fourth days of life and on their mothers; not a single child gave a positive reaction, whereas 71 per cent. of the mothers reacted positively.

Sucklings react but seldom. Tamayo Longo obtained a positive cutaneous reaction in a suckling fifty-two days old, whose foster-mother died of pulmonary tuberculosis on the fifty-second day *post partum*. In the first year of life the number of those who react varies according to the different statistics between 1 and 5 per cent.; it is the highest among children taken exclusively from very bad social conditions, who had shared the home of parents, foster-parents, or relations suffering from open tuberculosis.

With increasing age, after the first year of life, the number of positive cutaneous reactions increases and generally even in the fourth year becomes so frequent as to lead to the supposition of the presence of inactive tuberculosis. The environment of the children causes great fluctuations; while children of the poorer classes react to the extent of at least 20 to 30 per cent. of the total number to the first cutaneous test, only about 5 per cent. react of the children of well-to-do parents.

**and with Clinical  
Condition.**

A similar agreement is apparent when a comparison is made between the cutaneous reaction and the clinical condition.

Of clinically tubercular children in v. Pirquet's extensive case-reports 87 per cent. reacted, the remaining non-reacting cases of manifest tuberculosis being almost all cachectic, or in the last stage of miliary tuberculosis. Of the children clinically free from tuberculosis 20 per cent. reacted, rising from 0 per cent. in the first half year of life to 55 per cent. in the years from 10-14. According to Feer's investigations, of 1,732 clinically unsuspecting cases 0 per cent. reacted positively at the age of 0-6 months; 3.4 per cent. at the age of 6-12 months; 6 per cent., 1-2 years; 11 per cent., 2-3 years; 17 per cent., 3-5 years; 22 per cent., 5-7 years; 29 per cent., 7-10 years; 38 per cent., 10-15 years. The publications of Speck, Langstein, Aronade, Morgenroth, Siegert and others also show that sucklings who are clinically tubercular and not yet cachectic or have only a few days to live, react positively without exception, and that healthy sucklings from surroundings free from tuberculosis react negatively without exception.

From such agreement we may conclude that there is a practically invariable relation between the cutaneous reaction and tuberculosis in the organism of the child,



**Method of Performing Cutaneous Test on Children.** The method of the cutaneous inoculation in children is the same as in adults. It is advisable, however, to consider only quite typical papules as positive, and atypical effects of inoculation as negative, in the latter case repeating the test. Also, should the first cutaneous inoculation produce no reaction, it should be repeated after one or more days. Only when the second inoculation produces no result should the cutaneous test be characterized as definitely negative.

Also in children it is not possible to draw any conclusion from the nature of the papule as to whether the tuberculosis is initial or obsolete, active or inactive, progressive, or non-malignant. This detracts from the diagnostic value of the cutaneous reaction. But the consideration does not hold in the case of sucklings, in whom there are no inactive or healed tubercular processes, but only progressive tuberculosis can be present; and for the same reason it need very rarely be taken into account during the first year of life. But at this age, too, the cutaneous reaction is of greatest significance when it is negative; it then signifies the absence of tuberculosis.

We can, therefore, summarize thus:—

**Value of the Test.** In young children the result of the cutaneous test is of greater value the nearer they are to infancy; in sucklings the positive reaction proves the presence of active tuberculosis, the negative reaction the absence of the disease.

Of older children, many who react are clinically healthy, *i.e.*, are possessors of small, inactive foci. In these cases the positive reaction is of value only so far as it shows the presence of a latent tubercular focus somewhere, while the negative result here, too, is of greater significance; older children who do not react cutaneously are with great probability not actively tubercular. In any case, a positive cutaneous reaction in children over 5 years of age must not be estimated too highly.

Nevertheless, the special advantages of simplicity and absolute lack of danger make v. Pirquet's cutaneous reaction the diagnostic test *par excellence* in childhood. Its employment is to be recommended in every case in which tubercular trouble is suspected in a child and open tuberculosis is present in its surroundings. v. Leube specially emphasizes this in the interests of general prophylaxis against tuberculosis. The further question of the actual site of the tubercular focus, whether a glandular swelling, thickening of a joint, pulmonary focus, &c., is of a tubercular origin or not, is not answered even in childhood by



the appearance of a papule. Clinical indications and other criteria are essential to determine this.

**Warning  
against Faulty  
Interpretation.**

With this hint we want to warn practitioners against faulty diagnoses which appear to result rather frequently from too schematic an interpretation of the positive cutaneous test. It must always be borne in mind that although the cutaneous reaction is etiologically of great value in childhood, in sucklings and young children even demonstrating the presence or absence of active tubercular trouble, it does not determine with certainty whether doubtful affections are tubercular or not and still less makes a topical diagnosis of tuberculosis possible. For instance, one is not justified in diagnosing pulmonary tuberculosis from dulness at the apex of a lung or catarrh in the inferior lobe in a child who gives a positive cutaneous test; the focus giving rise to the reaction may be in some small gland. The fact must also be remembered that the cutaneous reaction may be absent in spite of previous tuberculosis when the antibodies have been absorbed by other means, *e.g.*, owing to measles. Engel [71] holds that this source of error is avoided in the intracutaneous test which, he states, gives a reaction under all circumstances in children with a tubercular infection.

**Percutaneous  
Test.**

If inoculation is refused, then the percutaneous method in the form of inunction of tuberculin ointment, recommended by Moro, may take its place; but it is less accurate than the cutaneous inoculation.

**Conjunctival  
Test.**

The conjunctival reaction has found no great vogue in children's practice, and rightly so. And it is highly advisable rigidly to avoid the conjunctival test in *early* childhood. At the school age, too, we would not advise its employment. However cautiously we go to work, carefully selecting the cases, excluding with the greatest care those who have had previous affections of the eye and having discovered no sign of scrofula, we get no small percentage of cases of disagreeable conjunctivitis with tendency to the formation of phlyctenulæ and other permanent injuries following the instillation. It should never be allowable to test conjunctivally whole schools or classes in order to throw light upon questions of tuberculosis, however important such questions may appear. In this respect the cutaneous and the conjunctival test cannot be placed on the same level; the former is absolutely without danger, the latter, even with the very greatest care, not without danger. In addition, the diagnostic



advantage of the conjunctival test is not very great. Even if it diagnoses more active cases than the cutaneous reaction, yet 30 per cent. of the inactive forms of tuberculosis still give a positive conjunctival reaction.

#### Subcutaneous Test.

The subcutaneous tuberculin test in childhood combines, according to Binswanger [101], the advantages of certainty and harmlessness. Its application is only considerably limited by the readiness with which little children develop from various causes a rise of temperature, thus making it very difficult to decide whether febrile reaction is present or not. This applies specially to sucklings and to out-patient practice. To this must be added the reluctance of the parents or relatives of the children to sanction an "injection," so that, at present, the subcutaneous tuberculin test is limited for the most part to older children and private institutions.

One positive subcutaneous tuberculin reaction in a child does not allow of any far-reaching conclusions as to the character, extent and prognosis of the tubercular process. Engel tried to supply this deficiency by repeating the same dose after the reaction, increasing it later and even applying it several times. He thinks to differentiate between favourable and unfavourable tuberculosis by the greater or less susceptibility to tuberculin, and specially to determine or exclude progressive processes, pulmonary disease or latent tuberculosis. Latent localized glandular or scrofulous tuberculosis will, he says, react only once or twice to an injection of 1 c.mm. of tuberculin and in a short time fail to react even to larger doses. And children who react several times in succession to tuberculin doses of 0.1 c.mm. and less and only with difficulty or never become tolerant to this small dose, may be strongly suspected of pulmonary tuberculosis, even in the absence of any physical signs proving this to be the case.

Engel's observations seem to be noteworthy in so far as they allow of the conclusion that in childhood, when tubercular conditions are not so complicated as in adults, we have in the subcutaneous tuberculin test a means of distinguishing between latent and progressive tuberculosis. This would make the subcutaneous tuberculin diagnosis also valuable in the prognosis of tuberculosis in children. In any case, Engel's method must stand the test of time in the children's hospitals and sanatoria.

In practice the application of the subcutaneous method will be reserved for those children suspected of tuberculosis, in whom the cutaneous test has not removed all doubts as to diagnosis. If in such cases there should be fever or some other contra-



indication of the subcutaneous method, then the needle track reaction of Escherich with certain precautions should be considered.

For patients at the age of puberty, the cutaneous test becomes considerably more uncertain and unserviceable owing to the large percentage of inactive tubercular foci. The conditions for reaction are similar to those in adults; both a positive and negative result of the test have only a conditional diagnostic value. Therefore the same diagnostic measures are necessary in puberty as for adults.



### III.—The Specific Treatment of Tuberculosis.

---

#### A.—General Section.

**The Search for a Specific Remedy.** THE search for a specific remedy against tuberculosis is as old as the history of medicine itself. A host of drugs has been recommended for the purpose. So far as any of them possess value in symptomatic treatment they will maintain a place for themselves to deal with particular symptoms or to influence the metabolism in general. But there exists no drug to which can be credited a specific action against tuberculosis. With the discovery of the tubercle bacillus it became possible to test the bactericidal action of chemical agents directly, but the agents in question, introduced in various ways into the body, are either too much diluted to exert a sufficient action on the tubercle bacillus in the tissues—assuming that the contact with the affected tissue lasts long enough—or there is danger of damaging the tissues themselves. The latter factor comes into consideration in the introduction of drugs direct into the lung. R. Koch himself, through nine years of continuous labour, tested a countless number of chemical and pharmaceutical substances for their power of destroying tubercle bacilli in the organism. The result was negative. Just as little right to be regarded as specifics have the intravenous injections of balsam of Peru, of cinnamic acid or of cinnamate of soda proposed by Landerer. Nor need we consider here the organotherapy, with its reputed specific preparations of lung tissue, bronchial glands and lymph-gland juice; nor the zomotherapy of French authors, who believe they have found a specific remedy in muscle plasma; nor the hæmotherapy by means of the blood of supposed refractory animals, to which reference will again be made under the heading of “Serum Treatment.” A chemotherapeutic method, started by Finkler with chlorides and iodides of methylene blue and with lecithin and copper compounds, is still in the stage of early



experiment. v. Linden seems to have succeeded in showing by animal experiment that these chemical substances are able to penetrate to the tubercular tissue and the tubercle bacilli. This has sufficed to induce some enthusiastic therapists to use the preparations for human tuberculosis; Meissen in pulmonary tuberculosis and Strauss in external tuberculosis and lupus claim to have obtained satisfactory results. However, it is advisable to consider the objections put forward at the International Congress on Tuberculosis, held in 1912 and at the Eighty-fourth Meeting of German Scientists and Doctors, and for the present to remain sceptical and reserve judgment.

Tuberculin therapists have been reproached with being in opposition to the physical-dietetic methods, with underrating the results obtained by them and with attributing every success to tuberculin alone under the influence of blind enthusiasm. This is not correct. Even the most prominent representatives of the specific treatment of tuberculosis have always acknowledged that the hygienic-dietetic treatment, according to the principles of Brehmer and Dettweiler, showed the curability of tuberculosis and must remain the foundation of the specific treatment. Believers in tuberculin are aware of the importance of understanding the constitution of the patient, both in individual cases of tuberculosis and generally in the campaign against tuberculosis; they are aware too of the influence of climate, of the open-air cure, of hydrotherapy on the catarrh and inflammatory processes which accompany pulmonary tuberculosis, and they value these factors; they know the value of nutrition, they take metabolism into consideration and improve a poor condition of the blood; they make extensive use of various methods of stimulating up the system, such as baths, douches, massage, active muscular exercises at not too early a stage, and gradually increased out-of-door manual work. But in so doing they do not abstain from a direct attack on the "nox"—the tubercular virus—and on the focus of the tubercular disease.

The hygienic-dietetic treatment is a purely constitutional treatment; it aims solely at the increase of the natural powers of resistance of the diseased organism, by which means it shall be strengthened and healed. That this may succeed and that it very often does so in initial cases, no longer needs proof; sanatoria owe their existence to the discovery of this fact. But in more severe cases this method fails only too frequently, altogether in the short "cure" usual in public sanatoria. An improvement is attained, perhaps even the disappearance of the subjective symptoms, generally a truly astonishing increase in weight takes



place and also a temporary increase in bodily power; but, as a rule, the objective condition of the lung remains unchanged. The specific treatment, on the other hand, by inoculation of immunizing substances, takes effect on the diseased tissue and produces results which are immeasurably superior to those of the hygienic-dietetic treatment alone.

#### **Tuberculin**

#### **Treatment a**

#### **Natural**

#### **Healing Method.**

It is not without cause that lately tuberculin treatment, and with it all active immunizing procedure, has been reckoned one of the natural methods of healing; the substance injected into the organism is nothing foreign to the body, it helps it to form the antibodies, which it is not itself able to produce in sufficient quantity; by the biological production of the natural means of defence the specific treatment only imitates and assists the spontaneous processes of self-healing. This is proved by Löwenstein and Pickert's method of testing tuberculin immunity by means of mixtures of tuberculin serum ([19] and [18]). These authors were able to prove that the serum of individuals not specifically treated and suffering from pulmonary tuberculosis taking an extraordinarily favourable course, possesses the same tuberculin-neutralizing bodies as the serum of patients treated with tuberculin—a proof that tuberculin treatment is, in the best sense of the word, a natural method of healing, only imitating the natural course of cure.

#### **Tuberculin**

#### **and**

#### **Sanatorium.**

The tuberculin method does not set itself up in any way in opposition to other methods of treatment. In the less severe cases these may suffice to bring about a cure without tuberculin, but in other cases, especially the severer ones, tuberculin treatment cannot be dispensed with. In any case the increase of the general strength is a necessary premise, and that this is most rapidly and best achieved in the favourable hygienic conditions of a sanatorium, goes without saying. The tubercular patient will only get the greatest benefit from specific treatment by using to the full all hygienic-dietetic curative measures under the constant supervision of the physician.

Where the combination of these two methods is not possible, one is obliged to try and do as much as possible with tuberculin alone, and certainly more will be achieved with it than with most other methods of treatment used alone. And it will generally be possible in out-patient practice to obtain, either fully or partially, care and good food and the use of other curative factors—air, water and light. In any case, the practitioner, when using



tuberculin, must never neglect the hygienic-dietetic *régime*, which will prove of the greatest assistance in increasing and establishing the success of the specific treatment. On the other hand, tuberculin should not be used when the personal or social conditions are so unfavourable that harm to the organism may result.

## 1.—GENERAL PRINCIPLES OF TUBERCULIN TREATMENT.

The therapeutics of tuberculosis, based on its etiology, begin with Koch's tuberculin. In the theoretical section it has been shown how the difference in the site of inoculation of an experimental animal on the first and second infection led to Koch's discovery of the preparation. The guinea-pig has, through the first tubercular infection, already attained such a degree of immunity that the second infection obtains no hold.

### Further Observations on Guinea-pigs.

Koch found, further, that sterilized cultures of tubercle bacilli rubbed up in water and injected, even in considerable quantity, into healthy guinea-pigs, not only gave rise to suppuration, but that in tubercular animals very small quantities of the same cultures sufficed to kill within a short time. Their lives, however, may be saved by the repeated methodical use of high dilutions, and obvious improvement obtained. When emulsified bacilli were employed it was found that they were not absorbed at the site of injection, but remained a considerable time unaltered, giving rise to a local abscess. The curative substance must then be dissolved out by the body-juices bathing the bacilli, whilst the substance giving rise to abscess formation remains behind apparently in the bacilli, or is only very slowly dissolved out.

The attempt to extract this curative agent from the bacilli led Koch to the discovery of tuberculin. His recommendation of it in treatment he founded on its specific action on tubercular guinea-pigs and also on his observations with lupus patients.

### Koch's Discovery of Tuberculin.

In Koch's fundamental researches [3] it was at once clear that man was immensely more susceptible than the guinea-pig to the action of the remedy. Whilst a healthy guinea-pig stood a dose of 2 c.c. or more subcutaneously without perceptible harm, one of 0.25 c.c. suffices to produce an intense action in a healthy adult man. Estimated in proportion to body-weight,  $\frac{1}{12000}$ th of the quantity producing no perceptible action in the guinea-pig gives a marked result in man.

### Koch's Original View of the Action of Tuberculin.

With regard to the specificity of the action of tuberculin on tubercular tissue Koch has stated his view more exactly. He expressly emphasizes that tuberculin does not kill the bacilli present in the tissues, but that the tissue alone which encloses



the bacilli is affected by the action of the remedy. In this occur well-marked circulatory disturbances and great metabolic changes, resulting in some parts in necrosis and casting off of a slough, in others rather in the disappearance, a kind of melting, of the tissue. The remedy can only influence living tubercular tissue; on dead caseous, necrotic tissue it has no action.

It is important for the proper understanding of his original method of treatment to appreciate Koch's view of its action.

Since tuberculin causes necrosis of tubercular tissue and only acts on living tissue, the explanation is easy of why it may be given in rapidly increased doses. One must suppose that at first much living tubercular tissue is present and that a small dose of tuberculin suffices to cause a severe reaction. But by each injection a certain amount of tissue capable of reaction disappears and relatively larger doses are necessary to attain the same grade of reaction as before. At the same time, a toleration may make itself felt within certain limits; but when the initial dose can, in the course of three weeks, be increased five hundred fold, this cannot be held to be merely toleration, since there is no analogy for so rapid and extensive an adaptation.

#### **Koch's Original Method.**

In cases of tuberculosis of the skin, glands, bone and joints, 10 c.mm. were given as an initial dose, and one or two weeks later, after the reaction had died away, the dose was repeated and persevered with until the reaction ceased. In the case of phthisis the same dose was used at first, but later reduced to 1 c.mm. If fever resulted from the injection the same dose was repeated daily until no reaction followed; then the dose was raised to 2 c.mm., until this also was borne without reaction, and so on. But a certain number of more vigorous phthisical patients were also treated with large initial doses or with a rapid rise in the dosage.

#### **Its Results.**

From Koch's own statements, patients in the early stage of phthisis were all entirely relieved of symptoms of disease in the space of four to six weeks, so that they could be regarded as cured. From these observations he concluded that early phthisis was curable with certainty by means of tuberculin. In advanced cases notable improvement was attained; little or no result was achieved in the severer forms with cavity formation or secondary infection. Koch preferred the carrying out of tuberculin treatment in sanatoria to that in patients' homes, and set special value on the combination of tuberculin with climatic, open-air, and dietetic treatment.

#### **Emphasis on Early Application.**

The most essential point of the new method, however, was in its earliest possible application; the early stage of phthisis is the proper object of treatment, which can then exert its full and complete potency. Hence Koch exhorted practitioners, by all means at their disposal, especially with the help of examination of the sputum, and in doubtful cases by the diagnostic injection, to diagnose tuberculosis at the earliest possible moment. "The new method will only become a true blessing to suffering mankind when, as far as possible, all cases of tuberculosis come to early treatment and when severe neglected cases no longer occur, the latter up to now forming an inexhaustible source of ever fresh infection." This exhortation has not, even to-day, lost its fundamental truth, and merits still to be taken to heart,



**Exaggeration of its Value.** In this short summary of Koch's first publications appear the now obsolete views which guided the administration of tuberculin in the first tuberculin era. The astonishing cures in the case of lupus and other forms of tubercle led to an over-estimate of the curative power of the remedy. With misguided but intelligible enthusiasm, advanced cases were treated with too large doses, resulting in too severe reaction, and obvious and severe injury resulted from the faulty method of application. Koch had warned against it in vain. An additional factor was present

**Harmful Results:** and influenza was not then fully recognized. It was principally morbid anatomists who recorded harmful results, with Virchow at their head, and to him has been ascribed the credit of bringing the first tuberculin era to an end.

**These also Exaggerated.** The unfavourable reports of that time were undoubtedly exaggerated. In Koch's institute, at any rate, similar experiences were not encountered. It must also not be forgotten that *post-mortem* observations on patients who had been treated with tuberculin have only a qualified value. They were either cases in which the course of the disease could not be arrested by the tuberculin treatment and where the latter was therefore ineffective, or at best of those who after an originally favourable course of treatment had a fatal relapse, and consequently in whom the curative effect of the tuberculin was scarcely, if at all, to be recognized. If the morbid anatomist is to judge of the action of tuberculin *per se*, it must be in cases which have been so treated for a long time and have then died suddenly or of intercurrent disease.

**Pioneers of the Modern View.** The credit of holding fast to the established value of tuberculin and bringing it again to merited recognition is due to a small band of workers. We may mention the practitioners, Goetsch, Hager, Krause, Thorner, and in the front rank Carl Spengler and Petruschky, of whom the latter has been untiring in his advocacy of tuberculin in speech and writing. What the morbid anatomists had seen to be the dangerous feature in the action of the tuberculin at its inception was the stormy reaction, which on the one hand gave rise to dangerous destruction of tubercular tissue and on the other, by setting free the tubercle bacilli, might lead to extension of the tubercular process and a



transference of disease germs to other organs. This gave the indication materially to reduce the therapeutic doses of tuberculin and, as far as possible, to avoid reaction.

**The Mild Method  
of  
Administration.**

This mild method of administration was inaugurated at the same time, but independently, in 1891 by Ehrlich and Guttman [143], Lichtheim [144], Aufrecht [145], Biedert [146], and by Petruschky [147], who employed it for years in the out-patient department of Koch's Institute. In 1901 it was again brought to the front by Goetsch [148], whose recommendation was based on the permanent arrests which he had obtained with it, and it is with his name that the method has been generally associated. This reactionless method of injection characterizes the modern tuberculin treatment and has the following advantages over the old procedure:—

(1) It fulfils the first axiom in all medical treatment—*nil nocere*—and at the same time cuts the ground from under the opponents of the method.

(2) It is in accordance with the demand to avoid reaction by using the minutest doses and yet allows the highest and most potent doses to be reached.

(3) It extends the indication for tuberculin treatment by bringing the severer forms within its reach.

(4) It admits of the simultaneous and unhindered application of other well-proved methods of treatment and may be carried out in out-patient practice without sacrifice of occupation.

We will now turn to a consideration of tuberculin treatment in general, regarding tuberculin as a single entity and discussing what is common to all its forms and characteristic of the treatment in general. The various preparations will be treated separately in a later section and their method of production, dosage, and special features referred to. This has the advantage of avoiding repetition. But another motive underlies this arrangement. In surveying the enormous number of successfully treated cases in the literature, the impression is at once gained that the choice of a preparation is a smaller matter than the manner of its application. And this is the method of careful individualistic treatment common to all tuberculin preparations.

**Differences in  
Various  
Tuberculins.**

Of course, all preparations of tuberculin are not of equal value; they are chiefly differentiated by their varying toxicity, which depends on their relative content of bacillary



secretions and extracts. This will be more fully discussed in dealing with the individual tuberculins.

Opinion is not so clear as to the relative curative power of the various tuberculins. Koch's principal preparations—old tuberculin, albumose-free tuberculin, new tuberculin TR and new tuberculin bacillary emulsion—represent, according to his own experience with animals and human subjects, progressive stages of improvement. Koch himself has not described differences in their effect on the diseased focus; nor have they been observed by others in animal experiment. All other tuberculins are made in accordance with the principles of Koch and are unessential modifications. The supposed improvements, at present unproved, consist chiefly in the removal of the non-specific parts of the tubercle bacilli and the culture medium. These are doubtless unimportant; Koch himself eliminated them in his last preparation—albumose-free tuberculin.

**Old Tuberculin**  
causes more  
**Hyperæmia than**  
the later

**Preparations.** But from our lengthy clinical experience we can point out an essential difference in the effect of Koch's preparations, which is this: Old tuberculin preparations cause more severe hyperæmia of the tubercular tissue than the bacillary preparations, the mild new tuberculin TR, the sensitized bacillary emulsion and the very active Koch's bacillary emulsion. The clinical effect of this is the appearance of much more severe local reactions at the focus of disease. And from this fact certain conclusions may be drawn as to the employment of the different kinds of tuberculin.

**Old Tuberculin**  
**Best for**  
**Diagnosis;**

It follows first of all that old tuberculin and albumose-free tuberculin, on account of the importance of the focal reactions produced, are the tuberculins *par excellence* for purposes of diagnosis. Moreover, whenever more active focal reaction is desired, old tuberculin will be given the preference as a therapeutic agent. This will be the case whenever the tubercular focus can be seen and felt, in tuberculosis of the skin, of the mucous membrane, of superficial glands, of the bones and joints, unless experience has shown, that another preparation has proved more successful, as, for instance, in tuberculosis of the eye, or when there is not any definite contra-indication to the production of severe reaction owing to the complication of another organic disease. We are thinking specially of laryngeal tuberculosis accompanying severe pulmonary tuberculosis.



and to  
Produce Severe  
Focal Reactions.

The use of old tuberculin preparations will also appear advisable in pulmonary tuberculosis—the most important localization of the disease from the point of view of the practitioner—when it is desired to produce severe reactions in a focus which is uncomplicated, well circumscribed and not too pronounced—perhaps after the insufficient effect of the less severe method of injections without reaction. The old tuberculin preparations—apparently albumose-free tuberculin particularly—are also specially indicated for cases with toxic general symptoms; on the ground of his observations, Meyer recommends the sensitized bacillary emulsion on account of its content of ready-made protective substances. On the other hand, the bacillary preparations are preferable when the more severe focal reactions are to be avoided, owing to compact infiltrations with a tendency to disperse and extensive processes over large tracts of both lungs in an advanced stage. Also it is well, as a precautionary measure, not to use old tuberculin where there is a tendency to severe and frequent pulmonary hæmorrhage, although we are not of opinion that tuberculin is conducive to hæmorrhage; we will give more detailed reasons for this recommendation later when considering contra-indications in pulmonary tuberculosis.

The indications are similar in the localization of tuberculosis of other internal organs when it is more or less difficult to diagnose accurately, although an undesired and severe focal reaction is less to be feared in the mild method and when great care is taken. Where a particular preparation has proved specially valuable in any particular localization, this will be described under the organ in question.

Bacillary  
Emulsion best  
for  
General Use.

Apart from the special indications just given, we consider the bacillary emulsion the most efficient of all the preparations and recommend it for general use, especially after previous treatment with old tuberculin preparations. We have achieved the best results with bacillary emulsion. We consider it the most efficacious of all preparations of tuberculin. It proved much the best in febrile cases (*cf.* Charts 23 and 24), although it cannot be denied that fever is a difficult thing to treat, requiring time above all things and the use of other auxiliary measures, such as rest and water cure. An individual immunized to bacillary emulsion gives no reaction even to the highest doses of old tuberculin, whether of the human or bovine type. This is a regular occurrence which we have often



verified. But an individual immunized to old tuberculin and bovine old tuberculin may still react to the same or even a smaller dose of bacillary emulsion (Chart 18). This is important in practice, inasmuch as when it is desired to continue or increase the influence of tuberculin in patients who have already received the maximum dose of old tuberculin, they can be suitably treated with bacillary emulsion. But in passing from old tuberculin to bacillary emulsion, the dose must be reduced. We shall return to this point later. This method of previous treatment with old tuberculin and final treatment with bacillary emulsion has proved of great service to us in many cases: after having attained toxic immunity one seeks to approach bacterial immunity.

**Preferably  
Preceded by Old  
Tuberculin.**

Previous treatment with preparations of old tuberculin can, however, be recommended for the following reasons: As the bacillary emulsion contains all the active principles of the tubercle bacilli, this preparation makes the greatest demand on the diseased organism. It is more difficult to attain immunity to bacillary emulsion than to any other preparation of tuberculin. In advanced cases of tuberculosis, even quite small doses produce very strong febrile reactions but no focal reactions—in contradistinction to old tuberculin. It is possible that there may be to some extent lytic reactions; in human beings this is very difficult to prove by experiment, but, in any case, increase of sputum and of bacilli is a very frequent, if not a regular phenomenon after reactions. The conception of bacteriolysis is certainly playing a larger part of late in the tuberculin reaction. If this idea of the procedure of bacterial immunization by bacillary emulsion is correct, then the fever is to be attributed to an absorption of the toxins set free by the destruction of the tubercle bacilli. Now we

**The Ideal  
Immunization:  
Simultaneous Pro-  
duction of Antitoxic  
and Bacterial  
Immunity.**

know that we must distinguish between tox-immunity and bacterial immunity, and tuberculosis itself is the best example of this distinction; tuberculin immunity does not mean immunity to tubercle bacilli. The ideal immunization would be the simultaneous production of an antitoxic and bacterial immunity.

**The Double  
Treatment.**

So if the febrile reaction produced by treatment with bacillary emulsion may be interpreted partially as a bacteriolytic process, then the fever caused by the dissolution of the bacilli could be effectively met by previous treatment with old tuberculin



preparations, toxic immunity being first created. However it may be with the complicated process of immunization in cases of tuberculosis, we have attained the best results by taking the treatment with old tuberculin preparations up to the maximal dose or to a relatively high toxic immunity (up to 100 or 200 c.mm.) and then continuing with bacillary emulsion.

The dosage of the bacillary emulsion can be increased much more rapidly, as it is tolerated infinitely better. It is not, however, absolutely necessary to go back to the initial dose usually given, about the hundredth part of the previous dose of old tuberculin being suitable. For instance, if one has given 10 divisions of dilution I of old tuberculin, then 1 division of dilution II of the bacillary emulsion may be used. If the maximum dose—10 divisions of old tuberculin—has been reached, then as a rule 1 division of dilution I of bacillary emulsion will be supported without reaction.

If, for some reason or other, a change is made in the preparation used when weaker solutions are being injected, then one need only go back to the tenth part of the previous dose, for example, from 1 c.c. of dilution III of old tuberculin to 0.1 c.c. of dilution III of bacillary emulsion.

We have published details of our results in statistical papers [149].

It is a matter of great satisfaction to us that the last researches of R. Koch on the therapeutic use of tuberculin in human beings led him, after all sorts of variations, to the same method as that recommended by Jochmann [150] at the Congress on Internal Medicine, held last year. The results agree in every detail with the system of treatment evolved by us after years of experimental, biological and clinical study. This has been proved to us to be the best and we have described it here in broad outline.

## 2.—METHOD AND GENERAL TECHNIQUE OF MODERN TUBERCULIN TREATMENT.

### Choice of Site for Injection.

The usual and most suitable method of administering tuberculin for therapeutic purposes is the subcutaneous. Koch has from the first recommended as the best site for injection the skin of the back between or below the shoulder-blades, alternately on each side; the skin can here be raised in large folds and there is less chance of a local reaction; usually, in fact, none at all. For the patient's convenience the forearm is often chosen, but the skin here is less readily raised in folds and there is more likelihood of painful infiltration. There is also the network of veins to be considered, since damage to the smaller venules may occur, and the tuberculin being more rapidly absorbed, as in an intravenous injection, gives rise to unexpectedly severe reactions. To protect against such unwelcome surprises it is a good plan to



insert the needle deeply and withdraw it somewhat before injecting. If many patients have to be inoculated, when undressing would take too long, we recommend the injections being made in the breast near the mammary glands, which only necessitates the opening of the clothes in front. We have convinced ourselves in the last few years by the treatment of several hundreds of patients that the injections can be well tolerated there and for the most part even completely without reaction. To avoid reaction the injections must be made into the loose subcutaneous tissue between cutis and fascia; those into the cutis are painful and may at once be recognized by the palpable bleb they produce; they are more likely to give rise to infiltration, with swelling, redness, and occasionally pain of a dragging character, which may extend up to the arm. Infiltrations vary very much; the more immunizing substances the preparation contains and the more concentrated it is, the more pronounced do they appear; earlier after injections of old tuberculin than after a non-concentrated preparation, with more intensity after BE than after TR. They depend mainly on the quantity of the less soluble substances in the tuberculin. Other conclusions cannot be drawn; they rest on unproved hypotheses.

**Carl Spengler's  
Site.**

It should be mentioned that Carl Spengler intentionally chooses the extensor surface of the forearm, with the object of obtaining a criterion for the repetition of the injections based on the greater sensitiveness of the skin. According to his numerous observations there exists an infallible relation between the local reaction in the diseased focus, a reaction often difficult to demonstrate in pulmonary tuberculosis, and the needle-track reaction; and this relation is to be interpreted as a parallel occurrence of chemotactic hyper-leucocytosis. The inflammatory reaction at the site of injection accordingly gives a clue to the intensity and duration of the focal reaction, and the latter demands a suspension of the injections until all the symptoms of reaction have disappeared. Sahli also emphasizes the importance of the cutaneous reaction at the site of inoculation, which appears to him most important in judging the condition of immunity.

**Cutaneous Reaction  
not Parallel with  
Focal Reaction  
in Lung.**

The principle of allowing oneself to be guided in estimating the action of therapeutic tuberculin treatment by the result of the cutaneous reaction (v. Pirquet's and needle-track reaction) would be justified if the strength of the reaction really were a measure of the reactive inflammation in the lungs. But such a



connection has not been confirmed either by us or by others. On the contrary, we have reason to think that cutaneous reaction and focal reaction are two phenomena quite independent of one another and are ever more inclined to believe that the degree of cutaneous reaction depends upon the general nervous sensibility to reaction of the individual. The more we have studied the conditions of cutaneous reaction during the last few years the less are we able to accept the proofs which Saathoff [97] tries to bring forward in support of this theory. There is no definiteness about it, no uniformity of interpretation; we learn this from the comparative observation of patients suffering from initial and from advanced tuberculosis, with acute and chronic processes, with favourable and unfavourable prognosis, with well-nourished skin and the reverse. Among our numerous tuberculin patients we have always some cases in whom almost every injection produces acute infiltration of the skin without any specially characteristic condition of the lung or the temperature curve. The best way to clear up this question is to observe such foci as are visible to the eye. For example, the occurrence of a needle-track reaction whilst a lupus focus remains completely without reaction or the reverse state of things is hostile to Saathoff's opinion. Moreover, we are acquainted with a whole series of cases in which individuals clinically perfectly healthy have given so severe a cutaneous reaction that Saathoff would place them in his Group I, who gave not the slightest general reaction to 10 c.mm. of old tuberculin. This proves:—

(1) That the parallel between cutaneous and focal reaction cannot be maintained.

(2) That it must appear impracticable to make the method of tuberculin treatment and still more a subtle dosage of tuberculin depend on the amount of cutaneous reaction. The practical drawback of clinging to the above unproved hypothesis lies for the patient in the continuous use of too small doses of tuberculin, which are of little effect and may lead to hypersusceptibility; we have the same state of things here as in the abandoned method of continual observation of the opsonic index.

Other efforts to employ quantitative cutaneous tuberculin tests for the choice and dosage of tuberculin in treatment (Autokratoff, White, van Norman, Züblin) have also proved without result and promise no better success for the reasons given above.

#### Asepsis.

It is advisable to cleanse the spot chosen with ether before the injection, and by this means a slight anæsthetic effect is also produced. The cleansing



is not absolutely necessary, as in a series of many thousands of sanatorium patients where no disinfection of the skin was carried out there was no single case of suppuration or local inflammation. In out-patient and club practice the puncture should, however, be covered up after the injection has been made.

The choice of syringe has already been discussed (*vide* p. 71).

#### Choice of Syringe.

The barrel should be as long as possible, so that the graduation is widely spaced. It will then be possible to read off twentieths with accuracy, and so guarantee an exact dosage.

#### Other Methods of Administration.

Of late years various reasons have led to an attempt to administer tuberculin in treatment otherwise than subcutaneously. These methods have been intravenous, intrapulmonary, by inhalation, by mouth, by rectum, percutaneous, and cutaneous.

#### Intravenous Method.

The intravenous injections of tuberculin were first made and recommended by Koch [39]. He found in his first researches into the agglutination of tubercle bacilli that the agglutinating power possessed by the subjects of tuberculin treatment was to be interpreted as an immunizing process, and that in general a high agglutination value denoted a high grade of immunity. But it was a fact of regular occurrence that the agglutinating power of patients treated with tuberculin subcutaneously could be raised yet further by giving the same preparation intravenously, and this led to Koch's recommendation of the procedure. We [40] have shown that an immunity associated with extraordinarily high agglutination values is attainable by the mild subcutaneous method without the production of reaction, so that the chief ground for recommending the intravenous application is gone. In general, between the action of tuberculin intravenously and subcutaneously there is only a difference of degree and of time; with the former the reaction occurs very much sooner and it is more severe. But since the best results are to be obtained by the mild method and this, as has been shown, is eminently *the* method of administration, the intravenous application need no longer be considered.

#### Intrapulmonary Method.

The intrapulmonary method of application is the so-called lung-infusion of Jacob [151]. His aim was to bring medicaments with strongly bactericidal action on tubercle bacilli into the closest possible contact with the diseased area. This aim could be best attained by introducing a catheter into the commencement of a bronchus, after anæsthetizing the larynx and trachea, and applying a definite dose of the drug through it. The most favourable results were obtained with tuberculin. The desired contact of the diseased tissue with the tuberculin takes place under the most favourable conditions only to a small extent, and in any case is too brief for a direct action, since the drug is rapidly removed by the lymphatics. The method is

#### Criticism of Theory.

based on an incorrect conception of tuberculin action. We are rather in agreement with the pointed remarks of Levin [152] in this connection. He says: "The more or less crude attempts to improve on the inefficiency of our therapeutic endeavours by bringing the drug into direct contact



with the organ to be treated—*e.g.*, injections into the brain or spinal column, or into the air passages—do not take into consideration that a direct and material surface action is but little attained, since there are everywhere present lymphatics and blood-vessels, which quickly carry away the drug introduced. Even when at first a more intense action can be recognized, this is soon equalized down to the ordinary level. Instead of better action there often appears a worse one, on account of the damage to cell-life in such hollow organs due to the injection."

### **Tuberculin Inhalation.**

Kapralik and H. v. Schroetter [153] drew attention to the employment of tuberculin inhalation for producing immunity, after their researches had led them to believe that favourable results were to be obtained by this method. The proceeding is, in contrast to Jacob's, one free from danger, but there are no resulting advantages to recommend it. The principal disadvantages, on the other hand, are: Uncertain dosage of tuberculin; the using of enormous quantities of the drug while only the smallest quantities are effectively utilized; the necessary limitation to small doses, since on financial grounds the amount of tuberculin volatilized cannot be indefinitely increased. The possibility of applying tuberculin inhalation for purposes of diagnosis in accordance with these authors' methods we have been able to confirm but only with different and varying concentration [154 and 155]; the method appears to be too much bound up with unavoidable error to be trustworthy.

### **Oral Administration.**

The administration of tuberculin by mouth, which was first recommended by Freymuth, father and son, in the first instance for diagnostic purposes in the form of keratinized pills, is also, according to our own [155] and other recent investigations worthless (Huhs, Löwenstein, Köhler, Jochmann, Hell, Möllers, and Heinemann); for absorption from the alimentary canal is relatively inert, as is the case with snake poison and the toxins of tetanus and diphtheria. Thus tuberculin both *per orem* and *per rectum* produces no reaction in a tubercular guinea-pig (Laffert, Dieterlen). According to Ransom, physical factors are chiefly responsible for this result; all these albuminoid poisons pass the epithelial lining of the intestinal tract only with great difficulty, and are for the most part rejected; but if the protecting epithelium is injured or altered in any way, then absorption takes place. Besides this, the toxins are decomposed or attenuated by the processes of digestion, and the mechanics and chemistry of the stomach vary in different individuals. The result of this knowledge was the administration of the tuberculin in capsules insoluble in the gastric juice. So a series of new preparations arose, which, however, soon fell into well-deserved oblivion on account of their ineffectiveness and partly owing to their excretion unused

### **Action of Pepsin and Trypsin.**

through the intestines. Pfeiffer and Trunk were the first to prove experimentally that pepsin and trypsin exert a more or less extensive weakening or destructive action on tuberculin. At the instigation of R. Koch, B. Möllers and Heinemann [156] then undertook a detailed investigation, and by means of the tuberculin reaction, experiments on guinea-pigs and complement deviation, found that the specific active substance in tuberculin is so considerably damaged by pepsin and trypsin that the internal administration of tuberculin must be rejected owing to weakening of the tuberculin, incomplete absorption, and uncertainty of dose. Especially convincing are the recent tuberculin tests on tubercular guinea-pigs; those animals which



received intraperitoneal injections of tuberculin mixed with the digestive juices displayed no reaction and continued to live, while the control animals died with the typical phenomenon of "tuberculin death."

**Phtysoremid.** According to Calmette's investigations, it was supposed that effective action would be most likely with the internal administration of bacillary emulsion in the form of keratin-coated gelatine capsules; these Krause [157] gave, with exact instructions for use, to patients in whom regular injections were impracticable. The preparation is for sale under the name of Phtysoremid. But here, again, B. Möller's and Heinemann's experiments are unfavourable to the remedy; even with doses corresponding to 20 c.c. of the Hoechst bacillary emulsion, they could not produce a rise of temperature or other sign of reaction in their patients. Krause states that he has achieved visibly good results in glandular tuberculosis and has observed the healing of persistent fistulæ. Hager, too, mentions its efficacy in cases of surgical tuberculosis. Köhler obtained satisfactory results in less severe cases; in more severe conditions it failed, although thirty out of forty-two patients made an extraordinary and unexpected increase in weight, such as he had rarely observed in forms of the disease so unfavourably situated.

We purposely refrain from mentioning other and similar preparations for internal use which commercial speculation has brought into the market. There is not the slightest proof that their composition is superior, and there is no confirmation by unprejudiced, competent authorities of the good results always claimed for them. We specially call to mind the internal administration of tuberculin with guaiacum, creosote, iodine, arsenic, and quinine, which are sold under the scientific title of "chemotherapeutic treatment of tuberculosis." Such doubtful and uncertain remedies are certainly not needed for a rational combination of tuberculin and arsenic treatment.

**Administration per Rectum.** The rectal administration of tuberculin in the form of suppositories and enemata need only be mentioned here. There exists no indication for it; also experiments have shown that, just as in the oral method, the tuberculin is but slightly absorbed and in varying, uncontrollable amounts. It is a different matter when it is a question of the absorption of large quantities of serum, though nothing definite is known of the laws which govern absorption by the rectum and colon.

**Percutaneous Application.** An application *per cutem* has been employed by Carl Spengler in therapy in the case of very weakly phthisical patients with fever and hyper-susceptibility to tuberculin; mostly, in fact, children. The method has been, till now, but little taken up; Lips employs it in the same way as Spengler; Krause has seen no results from it. The view of the current text-books of physiology is that, in consequence of the fatty content of the normal epidermis and of the sweat glands, the skin is unable to absorb solid substances out of watery solution. Combined with fluids which dissolve and extract the sebaceous matter of the skin, certain drugs may be absorbed in very small quantity. This occurs, then, through the sweat glands or the interstices of the epidermal cells. When energetic rubbing is carried out there is a pressing of material into the pores and a mechanical loss of continuity between the epidermis cells as well as actual forcing into hair sacs and glandular ducts (*e.g.*, with mercurial inunction), in the same way as an inflamed skin with damaged epidermis absorbs more readily, the conditions more nearly resembling an ulcerated surface; energetic inunction



may lead to this result, and the efficacy of application *per cutem* can be thus explained. In any case the present teaching of physiologists with regard to the imperfect absorptive power of the skin needs revision.

**Münch's  
Method.**

Münch [158] and after him Poeppelmann [159] have used v. Pirquet's cutaneous inoculation with pure tuberculin repeated about every four to ten days for treatment. Wallerstein carries out an immunizing tuberculin treatment on the same principles, but using solutions as weak as possible. Sahli, too, has lately tried this method with a modification; he applies tuberculin in rapidly increasing concentration to scarifications on the skin of as equal a size as possible. As far as we know, no clear proofs of the value of these methods have been adduced.

The subcutaneous method seems to us to be the one which offers the great advantages of sparing the stomach, absorption in absolutely unaltered condition and the most exact dosage.

**Observation and  
Individualizing  
Necessary.**

With regard to the detailed mode of application, reference should be made to the Special Part, where this is discussed in detail in view of the intention of the book to serve as a practical guide to the practitioner; there will be found the initial dose, the increase of dosage, interval between injections, maximal dose, method of preparation and keeping. It need only be remarked here that the principle of application is a slow increase of dosage under the most careful observation and the avoidance to the utmost of severe reaction. No hard and fast scheme for dosage can be given, but each individual case must be considered for itself. Cases in which the disease is apparently of the same extent may behave in a radically different way towards tuberculin. Thus the treatment of a case in Stadium III with tuberculin may be an easier and more successful matter than one in Stadium I.

**Two Contrasting  
Methods  
of Dosage.**

As regards dosage two contrasting methods have existed from the first: the use of small and of large doses of tuberculin. The first tuberculin era was the period of large doses and severe reactions which at that time were identical. The endeavour to avoid dangerous reactions led of itself to a gradual reduction of the doses. To-day a whole series of authors claim to have been the first to recommend the avoidance of severe reactions. We have already pointed out the merit of Goetsch. From that time dates the beginning of the second tuberculin era.

Since then the principle has obtained of avoiding reactions as far as possible or only allowing slight reactions. There seems no sufficiently strong distinction drawn between the method which uses *only* small and the smallest quantities of tuberculin and by



so doing naturally also avoids reactions, and the mild, cautious method of gradually increasing the dose, aiming at the assimilation of large doses of tuberculin whilst avoiding reaction as far as possible and *beginning* with small doses. Moreover, it does not appear to be sufficiently known or emphasized that to-day the idea of larger doses of tuberculin has no longer anything whatever in common with the idea of severer reactions. Even Goetsch did not remain content with using small doses of tuberculin, but strove to attain a high degree of tuberculin immunity. This method is ours also, and is approved by R. Koch in his introduction when he says that "it is not advisable continuously to give only the smallest doses, as recommended in many quarters. It must not be forgotten that it is a question here of active immunization, and that it can only be of advantage to the patient that not too low a degree of immunity should be attained."

**Exclusive Use of  
Small Doses  
Not Justified,**

The first-named method—the exclusive use of small and the smallest doses—has not been able to produce any valid reasons to justify its existence. Nourney injects only the smallest doses at long intervals, in order to produce and maintain "Tuberculin Energy." His is a somewhat isolated position. Wright's method, which he built up into a system of his own, rests on the same principle of treatment and, as has already been stated, is being more and more abandoned. The

**owing to  
Production of  
Hypersusceptibility.**

continuance of the smallest doses is not very effective and easily leads to hypersusceptibility. We have already explained that, according to our experience, the production of hypersusceptibility in the course of tuberculin treatment has never been of advantage to the patient and that the essential nature of hypersusceptibility is not sufficiently understood to justify such far-reaching conclusions as to the therapeutic use of tuberculin.

In support of our standpoint, we would like to call attention to the experiences of the Leipzig Medical Clinic, given lately by Rolly [160]. Two hundred patients were treated at intervals of from five to eight days with the smallest doses of old tuberculin, beginning with '001 c.mm., and going up to '01 c.mm. The hypersusceptibility which regularly ensued prevented the dose ever being increased beyond 0'1 c.mm. The only good result was a generally appreciable increase in weight; an objective improvement in the condition of the lung was not attained to such a degree as to justify the assumption that the tuberculin had exercised a definite curative influence.



**Penzoldt's Results  
with Large,  
Cautious Doses.**

On the other hand, some recently published statistics of Penzoldt [161] speak in favour of large doses used with caution, and to these we should like to draw attention. They date from the first tuberculin era.

Nineteen years ago Penzoldt treated ten cases of tuberculosis of various stadia with large, carefully increased doses of tuberculin. Of these patients two died after fifteen to sixteen years, one from a relapse, the other from an unknown cause. Of the others only one underwent later a second cure, and all enjoy to-day a satisfactory or even good state of health quite equal to the demands of their calling, in some cases very severe demands. One of these cases Penzoldt had expected to prove fatal. Penzoldt demands that statistics should continue to be kept of such cases of tuberculin treatment as have been under observation for many years, so as to prove which is the best method of using tuberculin.

**Avoidance of  
Reaction.**

With regard to the action of tuberculin, a distinction must be made between the general reaction of the whole organism and the local reaction of the diseased focus. In the mild method of injection they only occur in a very much weakened form and it must be the aim to avoid severe reactions as far as is possible. The view must be entirely put on one side that the curative process in tuberculin treatment takes place only with objective signs of reaction. Clinical observation in cases of lupus and of laryngeal tuberculosis teaches that a local effect on the focus of disease may make itself evident by hyperæmia without a subjective feeling of illness or appreciable rise of temperature. The more gently the treatment is carried through, the slighter will be the evidence of local and general reaction. General toxic symptoms may occur with or without rise of temperature; these are tiredness, pains in the limbs and loss of appetite, and even in the absence of fever these are to be construed as a specific reaction. It is well to treat them as equivalent to a febrile reaction and to repeat the previous dose of tuberculin, when recurrence of the symptom is as unusual as a repetition of the fever. The conception of the tuberculin reaction must be wider than the one in current use.

With sufficient care it will then be possible in the majority of cases to carry through a course of tuberculin treatment to a finish without appreciable rise of temperature and without damaging the general health. But the susceptibility to tuberculin varies in different individuals, and treatment must therefore be strictly individualistic.

**Observation of  
Temperature;**

The more carefully doctor and patient watch the symptoms, the more easily will the course of treatment run without undesired interruptions. The common practice of observing the temperature curve only is quite



insufficient for the purpose. The effect of the tuberculin on the general health must also be carefully considered and noted.

It is advisable to carry out the observations of a case as follows: Each patient takes his temperature every two or three hours, preferably the former, and enters the observation in the form of a curve. The fever limit is  $37.3^{\circ}$  C. taken in the mouth; and the reading taken in the manner usual in sanatoria and with the necessary precautions may be regarded as absolutely trustworthy. Temperature not to be taken in the open air during cold weather. The patient is instructed to go to bed if this limit is appreciably exceeded or if he feels ill. Otherwise exercise suitable for his condition may be taken, and in any case confinement to bed is unnecessary. Any symptoms are to be noted by the patient on his chart, so that the influence of any particular injection on temperature and general health can be noted at a glance. This method applies specially to sanatoria, hospitals and out-patient practice, where a considerable number of patients attend for injection. In some few cases a special inquiry after symptoms will be necessary.

of other  
Symptoms:

Loss of Weight;

As a control the observation of the body-weight is of importance, and in some cases of the pulse. Loss of weight and sudden increase in frequency of a normal pulse are to be construed as the expression of an overdose of toxin, in the absence of other obvious cause. This overdose of toxin, as a rule, finds its expression in a hypersusceptibility to tuberculin, but it may also occur without fever. In any case, the occurrence of loss of weight must be carefully considered, and when it occurs no increase of the dose is permissible. It is advisable rather to increase the intervals or even return to a smaller dose, until the appetite, and with it the weight, improves again. In the same way the behaviour of the pulse is to be used as a control; a marked increase in the pulse-rate after an injection of tuberculin is an unfavourable symptom and demands caution. The next

Frequency of  
Pulse.

injection is to be delayed until the return of the pulse-rate to the normal, which, as a rule, takes place in one or more days. It must then not be a larger one, and pulse and dosage should thereafter be watched with particular care. With an unstable pulse an overdose of toxin must be constantly before the mind. On the other hand, we also see the accelerated pulse, which is so frequent a consequence of the absorption of toxins of the tubercle bacilli, become gradually slower in the course of tuberculin treatment. We have repeatedly observed a pulse-rate of 120 in the minute steadily fall to 80 in the course of six months (Chart 18). This is, however, not easily obtained, generally only by prolonged treatment with tuberculin.

The observance of symptoms must also be supplemented by



physical examination of the chest, its frequency of repetition being guided by the severity of the case and the course of the treatment and the result carefully recorded for the purpose of comparison.

For correctly estimating the individual susceptibility to tuberculin, more attention must be paid to the relative than the absolute rise of temperature. The control of the temperature is of the greatest importance in tuberculin treatment.

### **Registration of Temperature.**

It is advisable to register the temperature in the form of a curve. The waves in the curve in their relation to each other are of more importance than the actual elevation by so many tenths; and their observation is essential if the limit of reaction is to be approached as closely as possible. It is then much easier to judge when even a slight rise begins, reaches its acme and ends; and so to decide on the necessary interval, varying from case to case, and in so doing avoid the possibility of cumulative action. We therefore warn against taking the temperature only twice a day, and regard at least five times as necessary (at 8, 11, 2, 5, and 8 o'clock). In ambulant practice it should be taken at least four times (8, 12, 4, and 8 o'clock). No ambulant treatment without measurement of temperature!

### **Occurrence of Slight Febrile Reaction.**

The slightest rise of temperature must have subsided before the next injection is given. The dose must be the same as the previous one and only be raised after the temperature curve becomes quite normal. The behaviour of the temperature curve after the first injections is characteristic of the whole course and is therefore important for regulating the injections and dosage. But a sensitive temperature may occur only at the beginning of the course and soon disappear with correct technique, in the same way as slight fever may often be got rid of by continued repetition of slight reactions.

### **Aim to keep near the Limit of Reaction.**

The maxim to remain as close as possible to the reaction limit without well-marked or severe reactions occurring coincides with the experience that the most evident success has been obtained with slight reactions up to  $38^{\circ}$  C., or a little over. There is, on theoretical grounds, nothing to be said against this if proper precautions and oversight are observed, although the production of these slight reactions is by no means always to be ensured. The method will be more successful with some experience of tuberculin treatment. The beginner should lay special stress on the avoidance of reaction. Its practicability will also depend on the individual susceptibility to tuberculin, on the severity of the disease, and on the general constitution. The principle of the production of slight reactions will be more in



place and easier to carry out in slighter and more limited cases of disease, in the slowly progressive forms associated with fibrosis, where nutrition and appetite are good, where weight is being put on and the temperature normal and where the susceptibility to tuberculin is slight. But in these cases the possibility of an overdose must still be borne in mind.

**Cumulative Action  
and Hyper-  
susceptibility.**

We now come to the most important point in tuberculin treatment—the question of cumulative action and of hypersusceptibility to the toxin. It is only possible in the rarest cases to fulfil the demand to avoid febrile reaction altogether. Observing all precautions, fever will sometimes occur after an injection, which may last one or more days or even over a week. A pause of several days must then be made after the temperature has fallen, and the same dose then repeated. As a rule this repetition causes no further rise of temperature, or at any rate a slighter one; in the latter case the same dose should again be repeated, if necessary even a third time. But it may also happen that the repetition of the same dose gives rise to a higher febrile reaction than the first. This characteristic

**Diagnostic  
Significance of  
Cumulative Actions.**

phenomenon was described by Koch in regard to diagnostic injection of tuberculin and its significance in diagnosis utilized. A cumulative process was assumed, the rise of temperature being merely the expression of a summation of successive toxic effects. More modern is the explanation of the occurrence by a toxic hypersusceptibility. This plausibly assumes an increased susceptibility due to too rapid increase of dosage, deliberately aimed at within prescribed limits in the diagnostic application; in other words, it is due to an overdose of toxin. In tuberculin treatment the occurrence is altogether unwelcome and the most frequent cause of harm. If it is not

**Unwelcomeness  
in Treatment.**

sufficiently recognized and allowed for, a further reactionless course will not be attained: the continued repetition of the same dose, or a too tardy return to a smaller one, will only continue to produce severe febrile reaction and may lead to actual harm. In such a case it is best to allow a pause of eight or even fourteen days, to recommence with a much smaller dose and to proceed with redoubled slowness and caution. If the interpretation of the term *reaction* is the wider one already alluded to, including not merely the rise of temperature but other objective and subjective symptoms, it will generally be possible to recognize and prevent a threatening cumulation and overdose of toxin.



**Time of Injection.** For the time of injection we recommend, at variance with some other authors, the morning and not the evening, since febrile reaction of moderate degree may occur unnoticed during sleep and leave no trace on the following morning, with the result that the next increase in the dose may give rise by cumulation to high fever.

**Interval between Injections.** The interval between successive injections will be gone into more fully when the several tuberculin preparations are discussed. It need only be said here that the original method of giving a dose daily, which still has some vogue, is inconsistent with the mild reactionless method, since even febrile reaction may not make itself felt for twenty-six to thirty hours. Besides this, we know from experience with other immunizing methods that the organism requires a certain time for production of antitoxic substances after assimilation of toxin. The length of this incubation period varies for different toxins and is not definitely known for tuberculin, but practical experience of the summation of reactions indicates that daily injection is too frequent for even the small tuberculin doses. Analogy leads to the further conclusion that with increasing dosage the interval must be lengthened.

**Maximal Dose.** In considering the maximal therapeutic dose, a distinction must first be made between the absolute maximum, which will be considered under the several preparations, and the maximum for the individual. It must be the aim to approach the absolute maximal dose as nearly as possible in every individual case. But this must not lead to hurrying with the injections or the increasing dosage in order to complete the course in a given time. It must be constantly kept in mind that the curative effect for the individual is dependent not on the absolute, but on the relative size of the dose, *i.e.* that quantity of tuberculin is most advantageous which can at any time just be borne without reaction. This consideration is the likeliest to prevent the beginner from proceeding too rapidly with the dosage in the natural endeavour to provide the diseased organism with the maximum amount of antibodies. It must not be forgotten that in active immunization there are no ready-made antibodies for the patient to assimilate, but they must first be produced with the help of the toxins introduced. Rapid increase has, then, on the one hand, no curative value; on the other, the occurrence of severe reaction may affect the patient's general health, reduce his power of resistance for some or all



time, and, by producing hypersusceptibility, may stand in the way of the continuance of the course. With this knowledge the desire to complete the course within a specified time will not make us move from the prescribed lines. If in such a case the period

**Dosage must not be Hurried.** of treatment cannot be extended, it is always better to reach a smaller dose without reaction than to attempt to attain a higher one by violence.

The same applies to any very susceptible patient, no matter in what stage of disease; it is not so much a question of laboriously attaining a certain dose of tuberculin, as to ensure the assimilation of the doses given without undue exertion for the organism. Hence time must be allowed for the increase of dosage; the same dose repeated, if necessary, several times if reaction occurs, with increase of the interval; or, better, a return made to a smaller dose, increased again still more slowly. The thought guiding the technique must be that any dose associated with fever is too high for the individual concerned and that the smaller dose borne without reaction not merely suffices for therapeutic action, but is actually of more value. And to this view one must adhere when obliged for months to use only thousandths and hundredths of cubic millimetres, and when the end-dose perhaps does not exceed 1 c.mm. Tolerance cannot be attained by violence, but only by patiently persisting. Such grades of tuberculin susceptibility are, however, not common; they have been discussed thus fully on account of the greater difficulty in their treatment.

**Inadequacy of Minute Doses.** These considerations lead us to the question whether it is not sufficient or even better to be content with small doses of tuberculin or whether larger doses are the goal to be reached. We adhere to the principles enunciated by Koch for the several tuberculin preparations. If the basis of the modern view is accepted, that one aspect of the action of tuberculin rests on a systematically acquired tolerance, a gradually acquired immunity to the toxin, then the employment of larger doses of tuberculin cannot be dispensed with. And after what has been said it is clear that with this theoretical view the practical carrying out of a reactionless course of treatment is quite reconcilable.

**Length of Course:** We now turn to the question, how long the course of tuberculin treatment should last and with what final dose to end? The only answer of universal application would be—until the patient is cured, or as long as improvement continues. But it must be borne in mind from the outset that the duration of treatment is in



most cases neither in the command of practitioner nor of patient.

**In Sanatorium ;** Distinction must first of all be made as to whether the treatment is in a sanatorium or in general practice. In Germany the conditions in regard to tuberculosis among the working classes are: Members of that section of the community in which compulsory insurance holds must, when the condition of the lung is curable or capable of substantial improvement, be brought for a limited time into a sanatorium or health resort and a cure effected in this time. The severer cases and those for whom insurance is not compulsory remain under treatment by the general practitioner, or in some cases are treated for a while in hospital or in some voluntary institution.

**In Private.** In private practice the conditions are similar: The stay in the sanatorium is mostly a limited one, much too short to attain a complete cure; the patients return for treatment by their home doctor. In only relatively few cases is the patient in a position to complete his cure in a sanatorium or health resort under the eye of the one physician. All this must be considered with the question of the duration of tuberculin treatment. We must expressly emphasize here that we regard the treatment of active tuberculosis of the lung as a matter for the sanatorium, and tuberculin treatment as an essential part of sanatorium treatment in the majority of severer cases.

**Aim to reach  
Maximal Dose.** It must be our aim to reach the highest possible doses of tuberculin, to attain the maximal dose. In slight cases a cure will be effected in this way. If the limit of apparently possible improvement is not then reached, the maximal dose is to be repeated at increasing intervals of 8, 10, and 14 days, as long as improvement continues, in order to retain the toxic immunity as long as may be, to stimulate the production of antibodies and to assist the healing processes. This injection of the absolute maximum we have ourselves prolonged for many months in severe cases.

Weddy-Poenicke has lately recommended as the result of his own experience the prolongation of the intervals to three, four, and finally six to eight weeks, and believes that even breaks of three and more months would be possible and sufficient. We ourselves [162] have used this method of the injection of large doses at intervals of four to six to eight weeks with T.R. for many years.

The above-mentioned discoveries by Löwenstein and Pickert



of the neutralizing substances proved by them to exist in the serum and to be looked upon as antibodies to tuberculin, also point to the expediency and necessity of large doses of tuberculin. After injections of large doses of tuberculin, they observed the same regular phases taking place in the antibodies of the serum as in other processes of immunization. In consideration of the curve of the tuberculin antibodies, Pickert [18] insists on intervals of at least fourteen days in the injection of large doses of tuberculin in order to maintain the quantity of antibodies at a sufficiently high level to be favourable to the organism.

If susceptibility does not permit of the absolute maximum being arrived at, the individual maximal dose should be repeated and the attempt persisted in to raise the dose when possible still further, an attempt which may at any time succeed.

**After-treatment.** The further question must now be answered, what to do with the patient who is not yet cured when his time in the sanatorium has expired. The logical outcome of what has been said is the continuance of his tuberculin treatment at home. The fulfilment of this demand assumes that tuberculin should find its way widely into general practice. And there can be no doubt that it would be productive of untold good if every practitioner were to master the technique of tuberculin administration and employ it wisely. The whole aspect of the struggle against tuberculosis would then be altered.

**Sahli's View.** Sahli [163], too, has recently advanced the view that tuberculin treatment is properly a matter for the family doctor, and has expressed his conviction that tuberculin is destined to play a beneficent *rôle* similar to that of vaccination in small-pox.

He [164] adopts an extreme point of view in so far as he stands for the principle of the mildest tuberculin treatment without the slightest objective and subjective reaction and looks upon all methods which seek to obtain a manifest reaction as cutting both ways and dangerous. He continues the treatment for a very long period, sometimes several years. He does not wish to obtain regular immunity, but only an immunizing curative effect. He describes as the goal of the active immunizing treatment immunization to toxins, that is "the production of curative immunizing reactions by substances of little or no toxicity. These specific toxoid-like substances should possess the same haptophore groups as the corresponding toxins, but should be as free as possible from the toxophore groups which characterize these toxins." A very similar conception has lately been taken up by Vaughan [165].



Where a cure is not attained with the single course of treatment and the prolongation of the injections in the manner described is impracticable, the question must be considered whether a repetition of the course is in place, and if so, when. Definite rules cannot be laid down here. It will be advisable from time to time to test the susceptibility to tuberculin, taking this as a criterion of the measure of cure reached.

**Serial  
Treatment:  
Petruschky.**

A systematic method has been evolved by Petruschky [166] with his interrupted treatment; in this method the average duration of treatment necessary is two years, periods of two to three months during which injections are given alternating with pauses of three to four months. Petruschky [167] records "how Koch strained every nerve—evolved new tuberculin preparations, increased the duration of treatment and gave enormous doses—in order to ensure a cure in a single period of treatment, knowing full well how difficult it is to get hold again of a discharged patient. The result, however, was unsatisfactory, at any rate as a rule." Experiences such as these gradually led Petruschky to the systematic working out of his interrupted treatment.

**Criticism of this  
Method.**

We find ourselves in no irreconcilable attitude towards this system. Charts 13 and 14 illustrate just such a method with two periods of treatment, but they show also the different conception of duration of treatment and dosage which we hold. It is only natural that the sanatorium doctor, in common with all those in charge of in-patients, should seek to extend the first period of treatment as long as he is in a position to obtain any considerable improvement of the physical signs in the lung. But it cannot seriously be contended that the utmost attainable in the first period of tuberculin treatment is really reached by Petruschky's maximal dose of 50 to 100 c.mm. of old tuberculin, or 0.1 c.mm. of new. Such a final dose may suffice for a case of tubercular glands in a child or for one of closed tuberculosis in its slightest form, if the patient can, as in Petruschky's case, be kept permanently under control and undergo at any time one or more further periods of treatment. But the sanatorium doctor will be as little able to attain this with the patients of the insurance and friendly societies under the present *régime* as with private patients on economic grounds. But in all cases of open tuberculosis, as well as in all advanced forms, the curative effect of tuberculin is by no means exhausted with the maximal doses used by Petruschky. Our own prolonged clinical experience teaches



ever afresh that permanent success increases with the duration of treatment. All the examples in the temperature curves in this book show that the sputum does not disappear for a period of months with large doses of tuberculin, and these are typical cases. We cannot therefore recommend breaking off the tuberculin treatment in cases of the II and III Stadia at such low doses and postponing the continuation to a future time, quite apart from the fact that the incompletely cured patient is exposed to all manner of intercurrent affections. In their demand for the use of large doses of tuberculin, Engel and Bauer, as already mentioned, go much further than we do, on the ground of new research and clinical successes in the treatment of tuberculosis in young children in the Düsseldorf Children's Hospital. They were able to prove that with the quantity of tuberculin injected, the number of antibodies in the blood increased, and that all patients with a good quantity of antibodies made satisfactory progress and showed an appreciable retrogressive metamorphosis of the tubercular process. Also Jochmann and Möllers have recently proved that complement-fixing antibodies only appear in the serum when large doses are reached.

In a recent extensive treatise on the tuberculin treatment of pulmonary tuberculosis, Petruschky [168] has again revived his method and compares it with our own. Although he does not entirely agree with our view as to maximal dose and the treatment of hypersusceptibility, he agrees with us in the frequent necessity for the larger doses and the individualizing dosage according to the sensitiveness or insensitiveness of the patient in question. He rightly asserts that large doses need not always be reached, but expressly demands that there must be no kind of limitation in respect of the duration or final dose of the first period of treatment nor of the subsequent periods. Therefore, though we do not on principle exclusively recommend tuberculin treatment by the interrupted method, we agree with him in setting the greatest store on the first period of treatment reaching the maximum attainable.

**After-history of  
Tuberculin-  
treated Patients.**

We do not by any means underestimate or neglect after-treatment with tuberculin. The experience of our systematic investigation into after-histories shows only too well that the struggle for existence often prematurely annihilates the good done by treatment. After-treatment with tuberculin would doubtless avoid this in many cases. Therefore we want the assistance of practitioners in continuing in ambulant practice specific treatment commenced in a sanatorium or recommencing



it when necessary. All seemingly healed patients must from time to time be examined and tested to show whether their subjective or objective symptoms are such as to demand after-treatment. This after-treatment is also to be instituted in all severe forms of tuberculosis in which cure has not followed a single period of treatment. Whether the continuous repetition of the maximal dose already described or a repetition of the whole course—in one or several periods—is desirable, must be decided in each particular case. Anyhow, small doses will not suffice in severe cases for the repetitions either; we are here in complete agreement with Kraemer [169] that the after-treatment (*cf.* Chart 14) should reach the individual maximal dose.

**Value of  
Tox-immunity.**

We will refer here to a recent work of Schröder [170], in which he expresses his disagreement with our therapeutic principle of the tox-immunity of the tubercular organism by high doses of tuberculin. We have sufficiently shown the theoretical foundation of our standpoint and we shall shortly show that this system of treatment has proved the best in actual practice. Schröder asserts that patients who have attained tox-immunity are liable to severe relapses. We cannot leave this uncontradicted. Although in most of the cases quoted there is no question of high immunity at all, the experiences met with in a small proportion of the cases do not justify the generalization of such a verdict. As far as we know, Schröder has never made personal trial of our method. But there should surely be no one who has had more experience of it than we ourselves; and we can testify that in our cases so treated we have never observed severe relapses in any striking proportion. On the contrary, we have often enough witnessed changes for the worse just in those cases where tuberculin treatment could not be sufficiently prolonged owing to external considerations.

Jochmann [171], who in general adopts the same standpoint as ours—that the length of tuberculin treatment must depend “solely and entirely on the sum of the biological and clinical criteria”—thinks that the disappearance of the cutaneous reaction, with favourable clinical conditions, may be considered as an indication for the cessation of the tuberculin treatment and, on the other hand, the reappearance of the reaction on a subsequent test after some months as an indication for the beginning of the after-treatment. He therefore replaces Petruschky's subcutaneous after-test with the cutaneous test which biologically is essentially the same. There is only a quantitative distinction to be made between the two methods; to us the clinical after-test seems the most important and decisive.



The question also of the cessation of the first tuberculin cure when v. Pirquet's test becomes negative requires to be more carefully considered. Jochmann recommends previous treatment with old tuberculin up to, perhaps, 300 to 500 c.mm., until the skin fails to react to the test made with old tuberculin. At this time there is always a positive cutaneous reaction to bacillary emulsion. So treatment with bacillary emulsion must follow until the skin fails to react to this preparation also. But, according to our investigations, undertaken quite independently, this often happens with undiluted bacillary emulsion at a time when the presence of tubercle bacilli can still be proved in the sputum. We have observed this even after therapeutic doses of from 0.5 to 1.0 c.mm., when it would undoubtedly be too early to cease the treatment.

Lenhartz, Oppenheim, and Löwenstein and Pickert have already shown that the cutaneous reactivity generally dies away when a relative immunity is reached to the larger doses subcutaneously. Also from our own experiments, the cutaneous reaction of patients specifically treated behaves in every way similarly to the subcutaneous, as would naturally be expected; the cutaneous reaction to old tuberculin disappears earlier than that to bacillary emulsion, while patients immunized with bacillary emulsion no longer display reaction to old tuberculin.

### 3.—THE SPECIFIC REMEDIES FOR TUBERCULOSIS.

In discussing the various tuberculins, their origin and mode of employment, the three chief preparations which we owe to Koch, will be taken as a basis, and following on them a *résumé* given of other specifics which have obtained some vogue. These will be treated in the detail due to their relative importance and the place they have obtained in therapeutics, so that the reader may obtain a grasp of the whole subject in correct proportion.

**Active and Passive Immunity.** Distinction must at the outset be made between preparations which aim at producing an active immunity and those designed to produce a passive one. By active immunization is understood the change in the organism which results from the absorption of bacteria or their products, and which leads to the appearance of specific protective bodies (antibodies) in the serum. This form of immunization is therefore an indirect one, the organism having to prepare its own protective bodies and hence is called with Ehrlich active immunization. By passive immuniza-



tion, on the other hand, is understood the production of immunity by means of a specific serum. The organism appropriates protective bodies, ready formed by another individual; it has itself no effort to exert, the process being a passive one.

### (a) Preparations Designed to Produce Active Immunity.

#### (1) OLD TUBERCULIN (AT).

**Preparation.** The first tuberculin prepared by Koch, called "old" tuberculin to distinguish it from the newer productions, was prepared in the following way:—

Pure cultures of tubercle bacilli which had grown four to six weeks on 5 per cent. glycerine-broth were sterilized with the culture fluid by heating in steam for one hour and concentrated at a reduced temperature to one-tenth of the volume. After the steaming the liquid was removed from the tubercle bacilli by filtering.

**Nature.** Old tuberculin is not a true toxin nor is it a pure endotoxin. It contains essentially the soluble secretions of the tubercle bacilli (toxins) in 50 per cent. glycerine dilution and also the constituents of the bodies of the bacilli (endotoxins), extracted during the hour's heating and steaming by the alkali and glycerine contained in the culture broth.

**Preparation of Dilutions.** In sanatoria with laboratories, sterile graduated pipettes of all sizes are accessible and the dilutions may be made in various ways. From 100 c.mm. upwards, the dose is taken with a sterile syringe direct from the original fluid. For private practice the following method is to be recommended, the diluting fluid being  $\frac{1}{2}$  per cent. phenol solution.

**Stability.** We preface the instructions with the advice: the physician employing tuberculin in therapy should not seek to avoid the small amount of labour involved in preparing the dilutions himself. More and more workers assert that there is often a great difference between personally prepared and bought dilutions, in favour of the former. This is a question of weakening by keeping the ready-made dilutions too long in stock. This calls for care. If ready-made dilutions are bought, these must bear the date of preparation. Therefore we are anxious that all dilutions prepared under the inspection of the Farbwerke Hoechst shall be labelled with the date of preparation, and only supplied within a certain time according to



the concentration. We may note here that the 1:10 dilution of the original fluid remains unchanged, but that the stability of the weaker solutions decreases continuously according to the grade of dilution.

### Procedure.

A number of wide-necked stoppered bottles of brown glass and about 10 c.c. capacity are obtained. These are first sterilized by boiling. The contents remain sterile when protected from gross contamination, since the diluting fluid is  $\frac{1}{2}$  per cent. phenol. To ensure continued sterility, the bottles, when quite or nearly empty, are occasionally filled quite up with the diluting fluid, the stopper gently inserted and the whole inner surface of the bottle and stopper left until next used in contact with the disinfecting fluid. For the sake of simplicity the dilutions are all made with a 1 c.c. syringe.

Solution (1): 5 divisions (tenths) of the syringe from the original solution = 500 c.mm., plus  $4\frac{1}{2}$  syringefuls of the diluent. Then each syringe-ful contains 100 c.mm. tuberculin or

$$10 \text{ divisions} = 100 \text{ c.mm.}$$

$$1 \text{ division} = 10 \text{ ,,}$$

Solution (2): 5 divisions from No. 1 solution = 50 c.mm., plus  $4\frac{1}{2}$  syringefuls of the diluent. Then each syringe-ful contains 10 c.mm. tuberculin or

$$10 \text{ divisions} = 10 \text{ c.mm.}$$

$$1 \text{ division} = 1 \text{ ,,}$$

Solution (3): 5 divisions from No. 2 solution = 5 c.mm., plus  $4\frac{1}{2}$  syringefuls of the diluent. Then each syringe-ful contains 1 c.mm. tuberculin or

$$10 \text{ divisions} = 1.0 \text{ c.mm.}$$

$$1 \text{ division} = 0.1 \text{ ,,}$$

Solution (4): 5 divisions from No. 3 solution = 0.5 c.mm., plus  $4\frac{1}{2}$  syringefuls of the diluent. Then each syringe-ful contains 0.1 c.mm. tuberculin or

$$10 \text{ divisions} = 0.1 \text{ c.mm.}$$

$$1 \text{ division} = 0.01 \text{ ,,}$$

Solution (5): 5 divisions from No. 4 solution = 0.05 c.mm., plus  $4\frac{1}{2}$  syringefuls of the diluent. Then each syringe-ful contains 0.01 c.mm. tuberculin or

$$10 \text{ divisions} = 0.01 \text{ c.mm.}$$

$$1 \text{ division} = 0.001 \text{ ,,}$$

N.B.—If only a few injections are to be given and fresh solutions always required, 3 instead of 5 divisions of the next stronger concentrated solution may be taken, plus 2 whole syringefuls and 7 divisions of the diluent.

All the bottles must be labelled in ink in order to prevent mistakes, and the labels should be varnished over. All solutions must be kept cool and in the dark, best of all in a refrigerator.

### Sterilization of

### Dilutions.

Ruppel [172] gives an emphatic warning against heating the prepared dilutions in order to sterilize them. Undiluted tuberculin can be heated for a long time in the autoclave up to 150° C. without its specific effect being injured.



But in dilutions the effective substance is injured by heating, in high dilutions almost entirely destroyed. Our tests have shown that this is true in dilutions of a millionth and hundredth thousandth part of a cubic centimetre. It is, however, necessary to heat the dilution for a few minutes; mere boiling up does not weaken the effect of the highest dilutions used.

N.B.—A rule which is really self-evident but nevertheless often broken, is that when a number of injections are to be made, commencement should be made with the weakest solution, proceeding to the next stronger. But if a weaker solution has to be used after a stronger, the syringe must be cleansed by repeated rinsings with the diluent.

**Initial Dose.** In favourable cases in the first and second stadium (Turban), where the general condition and bodily strength is good and the mouth temperature does not exceed  $37^{\circ}$  C. during the day, a dose of 0.1 c.mm. may be used to begin with. If reactions follow even this dose, or if the temperature several times during the daytime has been above  $37^{\circ}$  C., the dose should be reduced to 0.01 c.mm. In the great majority of cases of good prognosis, including those of the third Stadium, it will not be necessary to go below this dose to start with; it has not been necessary in the case of a single patient in the sanatorium. On the other hand, Hammer has seen a severe general reaction occur even after a dose of 0.002 c.mm., and he recommends in such cases, which are clinically less favourable and of doubtful prognosis, to start with 0.001 c.mm.

**Sequence of Doses.** With small doses up to 10 c.mm. an increase of one or more divisions may be made at each injection, according to the degree of susceptibility shown; thus:—

0.001, 0.003, 0.006, 0.01 c.mm.

(i.e., Sol. (5): 1, 3, 6, 10 divisions).

0.015, 0.03, 0.06, 0.1 c.mm.

(i.e., Sol. (4):  $1\frac{1}{2}$ , 3, 6, 10 divisions).

0.15, 0.2, 0.3, 0.5, 0.7, 1.0 c.mm.

(i.e., Sol. (3):  $1\frac{1}{2}$ , 2, 3, 5, 7, 10 divisions).

1.5, 2, 3, 5, 7, 10 c.mm.

(i.e., Sol. (2):  $1\frac{1}{2}$ , 2, 3, 5, 7, 10 divisions).

If slight reactions occur no increase should be made, but the same dose repeated; if more severe reactions occur the interval should be lengthened or a smaller dose given, as has already been discussed in more detail. One point must be specially emphasized: on passing from 0.01 to 0.02 c.mm., from 0.1 to 0.2 c.mm., and from 1 to 2 c.mm., the dose would be doubled. These are, as a rule, the critical points where reactions first occur. This



relatively rapid rise is not of much importance with solution 4; but it frequently produces its effect in passing from 0.1 to 0.2 c.mm., more frequently from 1 to 2 c.mm., and from 10 to 20 c.mm. Therefore here it is advisable to increase the dose by only half a division, that is from 0.1 to 0.15 c.mm., from 1 to 1.5 c.mm., and from 10 to 15 c.mm. (See our directions as to the graduation of the syringe.)

If the rise from 10 to 15 c.mm. is well borne, from 20 c.mm. upwards an increase of one or more whole divisions at a time may be tried; thus:—

15, 20, 30, 50, 70, 100 c.mm.  
(i.e., Sol. (1):  $1\frac{1}{2}$ , 2, 3, 5, 7, 10 divisions).

From 100 c.mm. upwards at first an increase of only half a tenth of a division should be made; if no reaction occurs then a rise of one or even several tenths of a division may be made; thus:—

Original solution (old tuberculin)  $1\frac{1}{2}$ ,  $2\frac{1}{2}$ , 4, 6, 8, 10 divisions.

If reaction occurs the procedure already mentioned must be returned to. We have been induced to discuss the dosage in such minute detail as we have repeatedly been referred to for advice even by those versed in tuberculin treatment who have found difficulties in determining the best graduation to avoid, as far as may be, any reaction. And what has been said here for Koch's tuberculin applies also in principle to all other tuberculin preparations.

#### Concentration of the Dose Injected.

It is in general the practice to inject each dose in the concentration in which it is drawn into the syringe. By many, however, the injection of large doses (from about 10 c.mm. upwards) in small quantities of one or two divisions is avoided, in order not to excite local irritation; the injection dose is made up to 1 c.c. with normal saline. According to our observations, there is no necessity for such a precaution.

#### Interval.

With regard to the interval between the successive doses, they may in general be given twice a week. In the case of tenths and hundredths the interval may be reduced to one day; above 10 c.mm. it should be not less than three clear days; and with the larger doses of 100 c.mm. and more, four to seven days. Whenever the period of treatment allows we go on to 1,000 c.mm.

Chart 13 is a specimen of a course of tuberculin entirely without reaction.

Chart 14 is an example of a second shorter course in the same patient six months after completion of the first.



Chart 15 illustrates the method of small reactions, avoiding any considerable rise of temperature.

Chart 16 illustrates the fact that moderate reactions are not always to be avoided even with careful dosage and shows the procedure when such reactions occur (repetition of the same dose, increase of the interval).

**Maximal Dose.** The maximal dose may be repeated several times at increasing intervals; its repetition depending, apart from the patient's circumstances, on the physical signs. All that has yet been said applies only to cases which take a smooth and normal course. The general principles stated earlier will determine the absolute and the individual maximal dose and the procedure in case of reaction occurring.

**Original Tuberculin.** In connection with Denys' tuberculin, which will be considered later, it must be noted that Koch's animal experiments were carried out with tuberculin which had not been concentrated to one-tenth of its volume and to which he gave the name "original" tuberculin (TO); but these were not published. In 1893, Koch handed over this original tuberculin to Carl Spengler for further study in animals and human beings, and until Denys' publications Spengler alone made any communications with reference to original tuberculin. As definite good results have been obtained with the non-concentrated broth culture and since the preparation has been extensively used, especially in Belgium and Switzerland owing to its low toxicity, the firm Farbwerke Hoechst has met the demand for this original tuberculin and supplies it under the letter TOA (Tuberculin-Original-Alt).

This consists of a filtered culture of tubercle bacilli of human origin, not concentrated by boiling and completely free from the bacillary bodies themselves. It contains exclusively substances which have been produced by the tubercle bacilli during their culture, and abstracted by the culture fluid (toxins), whilst old tuberculin contains, besides these toxins, substances which are extracted from the bodies of the tubercle bacilli at a higher temperature (endotoxins). As it is not exposed to heat for an hour it is believed in many quarters that it contains the specific substances of tuberculin in an unchanged state.

1 c.c. of TOA corresponds to the 10th part or 0.1 c.c. of old tuberculin.

With this preparation we have treated about sixty cases in all stages. It is distinguished from old tuberculin by its lower toxic power, due, on the one hand, to its being ten times weaker; and, on the other hand, to the absence of the substances extracted



from the bodies of the tubercle bacilli. Patients who are immune to original tuberculin, sometimes react even severely to 50 c.mm. of old tuberculin. We have not noticed any superiority in its therapeutic efficacy to the concentrated tuberculin (*cf.* Chart 17).

**Vacuum  
Tuberculin.**

The Farbwerke Hoechst also prepare a form of TOA, concentrated at a low temperature under reduced pressure to 1/10 of its volume, the *Vacuum Tuberculin* of Carl Spengler. Vacuum tuberculin is quantitatively identical in action with TOA, its advantage lying only in the fact that it will keep better and longer.

1 c.c. vacuum tuberculin = 10 c.c. TOA = 1 c.c. old tuberculin.

N.B.—These three preparations are also manufactured in a similar way from cultures of the tubercle bacilli of the bovine type.

**Bovine Old  
Tuberculin.**

At the instigation of R. Koch, we have used bovine old tuberculin prepared at the Koch Institute on a large number of cases, curable or capable of improvement. Excellent results have followed its use, but in a material of nearly 300 cases of all stadia we have not been convinced that its curative effect is greater than that of tuberculin of human origin. Bovine old tuberculin doubtless possesses very considerably fewer toxic properties and has a milder action than the human tuberculin of analogous preparation (*cf.* Chart 18). It is as well borne as the above described original tuberculin (TOA). The non-concentrated bovine preparation—bovine original tuberculin—which we have also used, has a still milder action; this does not contain the extractive substances from the bacillary bodies.

## (2) ALBUMOSE-FREE TUBERCULIN (AF).

**History.**

Koch, shortly before his death, instituted experiments in the Rudolf Virchow Hospital with tuberculin grown on media free from albumose. This preparation was introduced as an attempt to avoid the fever caused by albumoses, for in susceptible patients anaphylaxis may be produced by the repeated injection of tuberculins rich in the latter. Albumose-free tuberculin is now prepared by the Hoechst Farbwerke in the following manner:—

**Mode of  
Preparation.**

Erlenmeyer flasks are filled with an albumose-free culture fluid (Koch's prescription: Potassium phosphate, 0.5; magnesium sulphate, 0.06; magnesium citrate, 0.25; asparagin, 0.5; glycerine, 2.0; soda, 0.25; distilled



water, 100 parts), inoculated with a pure culture of human tubercle bacilli and left in the incubator at 37° C. until the surface of the culture-fluid is covered with a thick growth of pure culture and the volume is reduced to  $\frac{1}{10}$  of the original quantity. As soon as this has occurred, the bacilli are killed by heating for two hours at 60° C. on two successive days and separated by continued filtration from the culture fluid. The latter, after the addition of 0.5 per cent. phenol for a sufficient length of time to kill any bacilli which may still be present, constitutes albumose-free tuberculin ready for use. It corresponds in all particulars to Koch's old tuberculin.

### Properties.

For two years we have made extensive tests with this new preparation and have treated several hundred cases with it. Our opinion as to its activity is that it is better tolerated than old tuberculin, even by very sensitive patients; that in the latter the treatment can be carried out to the end without trouble, while with the smallest doses of old tuberculin slight febrile reactions and disturbances of the general condition impede progress. Needle-track reactions are considerably slighter, infiltrations practically never occur. The absence of these general and local symptoms is probably due to the exclusion of albumoses and certain toxic substances which arise in the concentration of the preparation at high temperatures. The action of albumose-free tuberculin is not inferior to old tuberculin; but the larger, more active doses of the former are more easily and quickly reached, and as a successful tuberculin cure, at any rate in open pulmonary tuberculosis, cannot be made without the large doses, this is an advantage. The special merit of albumose-free tuberculin seems to us to be that, owing to the absence of certain toxic properties present in old tuberculin, it is particularly suitable for ambulant treatment, which will be the more easily carried out to the large extent we desire the better the tuberculin is tolerated and the less the reactions it causes. We have not observed an antipyretic action to any great extent; at any rate, in this respect albumose-free tuberculin is much inferior to bacillary emulsion; but the latter, in its character as an emulsion, is more likely to cause difficulties in ambulant practice.

### Activity.

In some quarters complaints have been made that albumose-free tuberculin is irregular in action and causes uncalled-for high febrile reactions. The explanation of these phenomena does not lie in any imperfection in the preparation itself, but in the insufficient knowledge of the constancy of its action. The original concentration to a quarter of the volume was given up owing to the poor durability of the preparation. Further experiments have taught that even in a concentration of one-tenth of the original volume a certain



instability is present during the first three months, sometimes one way, sometimes the other. After this it remains absolutely unchanged. Now this preparation is not only tested for toxicity under Government control on animals like old tuberculin, but its activity is also more exactly determined by the agglutination and complement-binding tests. The Hoechst Farbwerke further take great care that only constant preparations are put on the market.

#### **Dosage.**

The dosage of albumose-free tuberculin should follow the same lines as for old tuberculin. Chart 19 is an example of a completely reactionless course with a fairly rapid rise of dose. Chart 20 shows an equally favourable course with some slight febrile temperatures, the dose almost always being increased in spite of slight, negligible reactions. Loss of fever occurred.

#### **Experiences with Albumose-free Tuberculin.**

The experiences of Jochmann and Möllers [173] in about 150 cases of pulmonary tuberculosis of the first and second stadia with regard to the susceptibility to old tuberculin of patients treated with albumose-free tuberculin are worthy of note. They found, and we can completely confirm their observations, that this susceptibility is but little diminished by the previous treatment, presumably because old tuberculin possesses toxic substances extracted by heat which are not contained in albumose-free tuberculin. Patients immunized to 1 c.c. of albumose-free tuberculin react with high fever even to a twentieth part of old tuberculin. This is of importance in practice inasmuch as it is not advisable to follow up a course of albumose-free tuberculin with one of old tuberculin. On the other hand, after-treatment with bacillary emulsion is well borne and can be completed relatively quickly, since the sensitiveness to bacillary emulsion is diminished by previous treatment with albumose-free tuberculin, just as with old tuberculin.

At the Congress of Tuberculosis in 1911, albumose-free tuberculin was awarded an extremely favourable judgment, corresponding on the whole with our experience cited above. Beninde, Holdheim, Meyer and Sobotta all expressed their satisfaction with the preparation. Ziegler even stated that he obtained far better results than with any other preparation; he described it as mild and efficacious, specially valuable in reducing fever and gradually decreasing and finally eliminating tubercle bacilli from the sputum. He recommends it without reservation as the specific tuberculin in pure form, free from foreign albumin and organic extractives. Brecke emphasizes the absence of any unpleasant phenomenon following the injections, but, with us, holds that it is not yet proved more efficacious than the other preparations of Koch, especially bacillary emulsion. Landmann holds



that the one and only advantage of the preparation is that it is not heated during its manufacture.

Further confirmation on the above lines has been afforded by Freymuth, Ország, and Spitzstein.

### (3) NEW TUBERCULIN (TR).

For his later preparations of tuberculin, Koch [174] adopted a new method.

#### **Toxic and Bacterial Immunity.**

With old tuberculin the aim is the attainment of immunity simply against the bacterial toxin; on the bacilli themselves the immunity has no influence. The conditions are similar to the case of tetanus; the filtrate from the culture fluid contains the soluble products of the tetanus bacilli with their specific toxins; against this toxin the immunized animals are protected, but the bacteria themselves are unharmed, they continue to live and may eventually kill the animal after the tox-immunity has passed off. On the other hand, with cholera and typhoid it is a question of a pure bacterial immunity; the animals treated with fresh agar cultures are protected against the bacteria but not against the toxins secreted by them. Living bacteria are soon destroyed in the body of the immunized animal, although no one has yet been successful in immunizing the animals beyond a certain limited dose of toxin. Koch's aim was to combine both these forms of immunity in his treatment of tuberculosis. He thought he recognized a tendency towards immunity in the miliary tuberculosis of man and the experimental tuberculosis of the guinea-pig. A stage occurs in which it is extremely difficult to find any trace of the bacilli which were at first present in great numbers. It appears here to be a question of a real process of immunization against the bacteria, but one which is already too late. Koch aimed at obtaining this immunity at an earlier stage of the infection. The one thing necessary was to flood the organism with tubercle bacilli. Koch held that immunity usually did not take place because the tubercle bacilli are present in the tissues in such small numbers and grow so slowly. Where they multiply actively, *e.g.*, in lung cavities, they are thrown off unchanged and not absorbed at all. The process of immunization, therefore, did not occur. It only takes place when numerous bacilli distribute themselves rapidly in the whole body, as occurs in fact in miliary tuberculosis and the experimental tuberculosis of guinea-pigs.

#### **Preparation of a Tuberculin con- taining all the essen- tial Substances of the Bacilli.**

Koch's aim, therefore, was to ensure the absorption of as many unaltered tubercle bacilli as possible, whether living or dead. The attempt failed because the unaltered bacilli were not absorbed from the subcutaneous tissue, the peritoneal cavity, nor from the circulation, but gave rise to suppuration. He then made the attempt to obtain by chemical means, in a form which would be absorbed, all the substances contained in the tubercle bacillus as far as this was possible. By extraction with decinormal soda the preparation TA was obtained. This gave tolerable results, but it also contained some bacilli, which, although certainly dead, gave rise to abscesses. Finally, Koch obtained a complete breaking-up of the bacilli by grinding a well-dried culture without any addition in an agate mortar.



The powdered mass was then stirred up in normal salt solution and separated by centrifugalizing into two layers: an upper one TO, very similar to TA, and containing the glycerine-soluble substances; and a lower layer TR containing chiefly the substances left behind after extraction with glycerine.

### Properties of TR.

TR unquestionably possesses immunizing properties, as Koch demonstrated on animals and man. Considering reactions necessary in the case of old tuberculin in order to obtain any curative result, with TR he sought as far as possible to avoid them. The immunity is quite independent of reactions. The important point is, by gradually increasing the dose, to make the individual insensitive to TR, and, since this contains all the immunizing substances of a tubercle culture, at the same time insensitive to the tubercle bacillus. A patient immunized against TR, even in the practical absence of reactions, does not react to large doses of old tuberculin and is therefore immunized against all constituents of the tubercle bacillus.

In the process of immunizing healthy animals and treating infected ones it is entirely a question of assimilating the largest possible doses. Koch succeeded in this way in completely immunizing guinea-pigs, so that they stood repeated injections of virulent cultures without becoming infected. Even in the case of guinea-pigs which were in too advanced a stage of the disease for complete recovery, some grade of retrogressive changes could be demonstrated after treatment with TR.

### Indications and

**Contra-indications.** In advanced cases of phthisis, especially those with severe mixed infection and high fever, TR should not be employed. But in all other cases which Koch treated he obtained, without exception, striking improvement, far exceeding that with the old tuberculin; and among these were cases of lupus where ocular demonstration proved the healing process beyond dispute.

The original solution of TR contains 20 per cent. glycerine, which acts as a sufficient preservative. In practice the dilutions should be prepared in the manner already described; not with phenol, but with physiological saline or 20 per cent. glycerine; the latter lasts about a fortnight. It must not be forgotten in preparing the dilutions that TR is very like an emulsion and that therefore the bottle must be thoroughly shaken before removing the tuberculin.

### Initial Dose.

Koch's instruction is to begin with 0.2 c.mm., so small a dose that it is quite exceptional for a reaction to occur. If it does, a tenfold more dilute solution is prepared.



The dose is to be so slowly increased that elevation of temperature by more than half a degree is avoided. Febrile reaction must have completely passed off before the same dose is injected again.

**Sequence of  
Doses.**

To avoid repetition the reader is referred back to the very minute directions given in the case of old tuberculin. Chart 21, that of a patient with severe tuberculosis of the larynx combined with slight pulmonary disease and facial lupus, shows how rapidly the dose may be raised. But in principle the dose should be increased more slowly, since the rapid rise has no therapeutic advantage and may affect the general health to its detriment. On the other hand, TR does not require anything like the same precaution in its administration as old tuberculin; it is the mildest of Koch's preparations.

**Interval.**

The intervals are the same as with old tuberculin: at first every other day, from about 50 c.mm. upwards twice in the week, above 500 once weekly, and with the largest doses we have been in the habit of allowing still longer intervals.

**Maximal Dose.**

The maximal dose is 2,000 c.mm., which we generally repeat at increasing intervals of two, four, six, and eight weeks. Repetition of the maximal dose is always to be recommended, the interval varying from case to case. The low toxicity of TR makes it very suitable in all cases of great susceptibility to tuberculin. Hence it may be used in such cases, as Goetsch has advised, as a preliminary to a course of old tuberculin or of the bacillary emulsion.

We have recorded a considerable number of good results with this preparation [162]. One of the most noteworthy has already been alluded to. The patient was cured and has remained so for six years. The liability to deteriorate and the very high cost militate against its wider adoption.

#### (4) NEW TUBERCULIN BACILLARY EMULSION (BE).

After his agglutination experiments, Koch [39] modified his new tuberculin to the extent of no longer separating TO and TR. Instead of centrifugalizing, the comminuted bacilli, after being suspended in normal saline, were merely allowed to settle and 50 per cent. glycerine added for greater permanence.

**Koch's Agglutina-  
tion Experiments.**

Koch's experiments led to the result that it was better to employ the ground-up bacillary mass without separating into layers



and that high agglutination values were reached with the greatest certainty and speed when the dose was rapidly increased and severe reactions occurred. For these experiments Koch had at his disposal only very unfavourable material, which was scarcely eligible for sanatorium treatment. Hence his results, of which he gives a summary himself, speak all the more forcibly in favour of specific treatment with bacillary emulsion.

**The Mild Method  
of  
Administration.**

Our own researches [40] soon led us to avoid the mostly very violent reactions associated with Koch's method of rapidly increased dosage—reactions attended with much general disturbance—after the proof had been given that, even in their absence, high agglutination values could be obtained. This mild method of injection, borne very well by patients, not only met with Koch's complete approval but is now used by his pupils with the best results (Jochmann).

**Preparation of  
Dilutions.**

Bacillary emulsion is a suspension of one part of pulverized tubercle bacilli in 100 parts of distilled water, to which equal parts of glycerine are added; by this addition considerable stability is attained. The stock solution contains in 1 c.c. 5 mg. of solid substance.\* From 100 c.mm. upwards the dose for injection is taken direct from the stock solution. In practice the following method of dilution is recommended, the diluent being normal salt solution plus  $\frac{1}{2}$  per cent. phenol if the solutions are to be kept several days.

(With regard to the size of the bottles, sterilizing, labelling and storing them, the same applies as for old tuberculin.)

Solution (1): 5 divisions from the stock solution = 500 c.mm., plus  $4\frac{1}{2}$  syringe-fuls normal saline. Then each syringe-ful contains 100 c.mm., or

10 divisions = 100 c.mm.

1 division = 10 „

Solution (2): 5 divisions of No. 1 solution = 50 c.mm., plus  $4\frac{1}{2}$  syringe-fuls saline. Then each syringe-ful contains 10 c.mm., or

10 divisions = 10 c.mm.

1 division = 1 „

Solution (3): 5 divisions of No. 2 solution = 5 c.mm., plus  $4\frac{1}{2}$  syringe-fuls saline. Then each syringe-ful contains 1 c.mm., or

10 divisions = 1.0 c.mm.

1 division = 0.1 „

\* As for TR, the statement of dosage by solid substance is unnecessary and the doses are reckoned as before in cubic millimetres. In the future the Farbwerke Hoechst will adopt this method in their instructions accompanying the tuberculin.



Solution (4) : 5 divisions of No. 3 solution = 0.5 c.mm., plus  $4\frac{1}{2}$  syringefuls saline. Then each syringeful contains 0.1 c.mm., or

10 divisions = 0.1 c.mm.

1 division = 0.01 „

N.B.—As we have to deal here with an emulsion the bottle must be well shaken for some time both when making the dilutions and each time before us. Special care must be taken with the original bottle of tuberculin containing only 1 c.c. to see that the sediment, which, when it has been standing for some time, is somewhat adhesive and cannot be very clearly seen through the brown glass, is thoroughly shaken up.

**Initial Dose.** In favourable cases of Stadium I or II with good general health, an initial dose of 0.1 c.mm. may be given. If reactions occur, if the temperature of the patient easily rises or in cases of doubtful issue, then begin with 0.01 c.mm. One is very rarely obliged to go back to 0.001 c.mm. or less.

According to Koch's original instructions, given under the influence of agglutination determinations, the dose should be rapidly increased until well-marked reactions occur. Then the agglutinating power should be determined from time to time and be raised to its maximum by constantly larger doses at greater intervals. Since we have shown that immunity, frequently accompanied by extraordinarily high agglutinating values, may constantly be obtained by the milder method, avoiding reaction altogether, the chief argument for the marked reactions falls to the ground.

**Sequence of Doses.** Chart 22 shows a case of open tuberculosis of the second Stadium with fairly high agglutinating power. It is an example of the method of treatment with slight reactions and rapid rise of dose. A course entirely without reactions may also be achieved by following the directions given under Old Tuberculin; it is, however, more difficult, and greater care must be taken in the observation of all the principles laid down in the general section. The dosage may be somewhat as follows :—

0.01, 0.03, 0.06 c.mm.	} With one to two days' interval.
(i.e., Solution (4) : 1, 3, 6 divisions).	
0.1, 0.2, 0.3, 0.5, 0.7 c.mm.	
(i.e., Solution (3) : 1, 2, 3, 5, 7 divisions).	
1, 1.5, 2, 3, 5, 7 c.mm.	}
(i.e., Solution (2) : 1, 1½, 2, 3, 5, 7, divisions).	



10, 15, 20, 30, 50, 70 c.mm. (i.e., Solution (1) : 1, $1\frac{1}{2}$ , 2, 3, 5, 7 divisions).	{	With two to three days' interval.
Stock Solution (B.E.) : 100, 150, 200, 300, 400, 500, 600 c.mm. (i.e., Stock Solution : 1, $1\frac{1}{2}$ , 2, 3, 4, 5, 6 divisions).	{	With three to four days' interval.
Stock Solution (B.E.) : 800, 1,000, 1,200, 1,400, 1,600, 1,800, 2,000 c.mm. (i.e., Stock Solution : 8, 10, 12, 14, 16, 18, 20 divisions).	{	With four, six, and ten days' interval.

With susceptible patients, only increase the dose by 100 c.mm. at a time for the larger doses in order to avoid severe reactions. It is also advisable in such cases to lengthen the intervals, by which means the occurrence of reactions is more easily avoided. The noticeably slight increase in temperature with large doses in Chart 22 may be looked upon as immunity reactions; this is shown by the fact that in spite of increase of dose they become steadily lower. We consider 2,000 c.mm. as the maximum dose; larger doses are often not fully absorbed. The maximum dose may be repeated several times with pauses of from ten to fourteen days; the principles explained before hold good here.

#### Antipyretic Action.

The antipyretic action of T.R. and, in higher degree, of the bacillary emulsion has been emphasized on various sides. Krause [175] especially speaks well of the bacillary emulsion in this respect. He was able, with very careful dosage, to abolish fever permanently in all cases, even in country practice, under the most unhygienic surroundings imaginable; in some cases fever disappeared which had withstood all other methods of treatment for a year.

Our own experiences, too, are ever more favourable the longer we use the preparation. The abolition of fever often succeeds without noticeable reactions with the use of small increasing doses; it is only seldom that we are obliged to produce considerable reactions at intervals of from eight to ten days. For this method the destructive processes in the lung must not be too advanced, nor must severe mixed infection be present.

Chart 23 illustrates the rapid cessation of fever in a severe case of subacute caseous phthisis in which there had been high to moderate fever for four months. The antipyretic action is obvious even from the first doses, which were always raised by about one half without the frequent occurrence of the more severe reactions.



Chart 24 shows a more gradual cessation of fever in a chronic caseo-fibrous case with slight febrile symptoms. Here, too, the loss of fever was secured with continuous rise of dose without perceptible reactions. Only after complete loss of fever did a severe reaction occur when a rather large dose was given; the chart shows the method of procedure and how after a fairly long pause the same dose may be gradually tolerated.

**Bovine  
Bacillary  
Emulsion.**

Bovine bacillary emulsion is analogous to the bacillary emulsion from human bacilli, but prepared with the bovine type of bacillus. Between the two preparations we have not been able to recognize any difference in therapeutic activity nor any distinct difference in toxicity. This was very obvious from the mere fact that the bacillary emulsion from Koch's Institute, which we used for a long time, was sometimes prepared from human strains and sometimes from bovine without any characteristic differences being noticed in their use. Koch's own experiments had proved a difference of species between the living bacteria but not of their metabolic products and cell-substances; further, the preparation of bacillary emulsion in Koch's Institute was preferably performed with bovine bacilli owing to their conception of the harmlessness of working with the bacillary particles for the laboratory assistants. As a matter of fact, the use and action of bovine bacillary emulsion was thus both known to and practised by us before the publications of Carl Spengler, which we shall describe later.

(5) SENSITIZED BACILLARY EMULSION (SBE).

**Sensitized  
Bacillary  
Emulsion (SBE).**

At the suggestion of F. Meyer, the Hoechst Farbwerke have made a sensitized bacillary emulsion (SBE), the Hoechst "Tuberkulose-Sero-Vakzin." The production of sensitized tubercle bacilli, *i.e.*, tubercle bacilli rendered capable of fixation of complement, rests on the Behring principle of the weakening of an antigen by the addition of serum, which he first applied in the immunization of the guinea-pig to tetanus toxin. It is prepared with a tubercular serum of high value, which by its specific amboceptor (antituberculin) content is intended to destroy the toxic effect of the tubercle bacilli. The Hoechst tubercular serum contains, besides the antituberculin, agglutinins, precipitins, and bacteriotropins. By the action of the serum on whole and ground tubercle bacilli, the antibodies contained in it are anchored by the respective receptors of the bacilli. Insoluble compounds of bacillary substance and specific



antibodies are formed which are absolutely non-toxic to healthy and tubercular individuals and affect tubercular processes in guinea-pigs in a striking manner.

**Mode of Preparation.** This emulsion is made by the Hoechst Farbwerke in the following way :—

Well-washed and dried tubercle bacilli of the *typus humanus* are mixed with a quantity of the fresh tubercular serum, varying according to the amount of the specific antibodies. This mixture is left several days in the incubator at 37° C. and is then placed in a shaking apparatus with glass beads and shaken until in a sample tested no whole tubercle bacilli can be found. Then the crushed bacilli are separated centrifugally from the serum, washed with normal saline and finally worked up into a fine emulsion with 40 per cent. glycerine water, to which 0.5 per cent. of carbolic acid is added. The content of bacillary matter amounts as in the usual bacillary emulsion to 5 mg. in 1 c.c.

The Hoechst Farbwerke supply the emulsion in the original concentration and in 6 dilutions ready for use in descending powers of 10, from 1:10 to 1:1,000,000, made with 0.5 per cent. normal saline containing carbolic acid, in bottles of 1 and 5 c.c. The original solution and the dilutions can be kept practically for any length of time in a cool place, but free from frost and protected from light.

N.B.—If desired, SBE is also supplied from bacilli of the *typus bovinus*.

The sensitized bacillary emulsion is used subcutaneously. Contra-indications are cachexia, mixed infection, and lasting hectic fever caused by the latter.

**Dosage of SBE** The treatment is begun with 1 division of solution 6 (1:1,000,000) and the dose raised according to the usual principles, noting carefully temperature, weight and general condition of health. Should any signs of febrile or general reactions occur, the last dose injected is to be repeated.

The treatment is considered to be ended when  $\frac{1}{2}$  c.c. of the stock emulsion is borne without reaction and the clinical result is satisfactory.

**Results.** According to the extensive investigations of Citron, the advantage of using sensitized bacillary emulsion lies in the fact that the injections produce less fever and that the production of infiltration is reduced to a minimum. Ed. Meyer and Spiess have achieved good results with this preparation in the treatment of laryngeal tuberculosis. Cohn observed improvement in children after its use. Sawolshkaja used it in three cases with good results; in three others it had to be given up because it produced general, local, and focal reactions. According to Jochmann's comparative investigations, there is no difference in the clinical effect of ordinary and sensitized bacillary emulsion. With both preparations febrile



reactions could be avoided with caution and when the doses were rapidly increased, both produced fever.

We, too, have for some years made extensive use of sensitized bacillary emulsion, especially in the more advanced cases. We have used the same dosage as for Koch's bacillary emulsion and, when the length of treatment permitted, have increased up to a half or one cubic centimetre of the original solution (*cf.* Chart 25). We have seen thoroughly good clinical results with the preparation and can confirm the advantages claimed by Citron. We have not yet been able to recognize any superiority over Koch's bacillary emulsion, either as regards antipyretic action or in respect of curative power. We recommend previous treatment with sensitized bacillary emulsion and as soon as doses are taken from the original solution, Koch's bacillary emulsion should be substituted; the latter is also considerably cheaper. It is advisable as a precautionary measure to reduce the dose to one-tenth in changing from one preparation to the other.

Chart 25 shows the method of application of the preparation in a case of tuberculosis of the bronchial glands, febrile for three months, with closed pulmonary tuberculosis of the first stadium. Gradual loss of fever and clinical cure were effected by constant rise of dose (even rather forced in the case of the larger doses), with but one febrile reaction towards the end of the treatment.

#### (6) LANDMANN'S TUBERCULOL.

##### Preparation and Underlying Principles.

Broth cultures of highly virulent tubercle bacilli, after being freed from fat and finely powdered, are extracted with normal saline or dilute glycerine for some time at 40° C.; the deposit is repeatedly treated in the same way with fresh fluid at a temperature gradually increased from 50° to 100° C. The extracts are mixed and the total product concentrated *in vacuo* at 37° C. By means of this fractional extraction, Landmann [17] holds that all the toxins contained in the bacterial bodies are obtained without damage or appreciable loss, whether those extracted at a high or a low temperature. The insoluble residue of bacilli remaining behind, when suspended in water, is, even in large quantities, incapable of killing experimental animals. On the other hand, the preparation itself is fatal to guinea-pigs in a dose of about 0.1 c.c. The latter is now added to the broth which has been concentrated *in vacuo* as far as possible and filtered; the mixture is again filtered through porcelain candles, phenol added (5 per cent.) and then diluted until 1 c.c. is a lethal dose for a guinea-pig of 250 gm. That the advantages



of this original method are not merely theoretical is shown by the fact that the preparation on prolonged heating at  $100^{\circ}$  loses its action and 1 c.c. is no longer a lethal dose for a guinea-pig.

**Animal  
Experiments.**

This tubercular toxin, containing the toxins of the culture fluid as well as those of the bacterial bodies, possesses an advantage of no small magnitude—that of being quantitatively and qualitatively tested on healthy animals and the dose thus exactly determined. Landmann adopts the point of view that tubercle bacilli, like diphtheria bacilli, form genuine bacterial toxins, that as genuine toxins they produce in the animal body antitoxins and expects his tubercular toxin to form antitoxins by means of the healthy cells. With regard to the test of toxicity on healthy animals, he is opposed to Koch, who considers the peculiar characteristic of the specific tubercular toxin to be that it has no effect on healthy animals.

In a series of experiments Landmann succeeded, by treating guinea-pigs with tuberculol, in immunizing them not merely against a tenfold lethal dose of tubercle bacilli, but in curing with injections of tuberculol guinea-pigs first infected with double the lethal dose of bacilli. The control animals, without exception, died of advanced tuberculosis after four to five months.

**Clinical  
Application.**

In man the method of treatment is the same as with the other preparations, avoiding reactions as far as possible. But Landmann lays the greatest stress not merely on bringing the patients to the highest level of immunity, but on keeping them there, *i.e.*, prolonging the treatment, and we concur with this. He prefers an increase of one-half and only reduces this to one-third, one-quarter, or one-fifth when half is not tolerated.

The doses to be injected would be then as follows:—

Solution (5):  $\frac{1}{2}$ ,  $\frac{3}{4}$ , 1,  $1\frac{1}{2}$ ,  $2\frac{1}{2}$ ,  $3\frac{1}{2}$ , 5,  $7\frac{1}{2}$  divisions.

Solution (4): 1,  $1\frac{1}{2}$ ,  $2\frac{1}{2}$ ,  $3\frac{1}{2}$ , 5,  $7\frac{1}{2}$  divisions.

With intervals of from one to two days.

Solution (3): 1,  $1\frac{1}{2}$ ,  $2\frac{1}{2}$ ,  $3\frac{1}{2}$ , 5,  $7\frac{1}{2}$  divisions.

With intervals of two days.

Solution (2): 1,  $1\frac{1}{2}$ ,  $2\frac{1}{2}$ ,  $3\frac{1}{2}$ , 5,  $7\frac{1}{2}$  divisions.

With intervals of from two to three days.

Solution (1): 1,  $1\frac{1}{2}$ ,  $2\frac{1}{2}$ ,  $3\frac{1}{2}$ , 5,  $7\frac{1}{2}$ , 10 divisions.

With intervals of from three to five days.

Repetition of the maximal dose of Solution (1): 10 divisions,  
at intervals of seven, ten and fourteen days.



With experience in specific treatment, this scheme can be modified according to the individuality of the patient. The maximum dose should eventually be used for several months until its highest therapeutic action has been attained. When necessary a second course of treatment can be begun after six months' interval.

### Results.

Landmann reports good results in open tuberculosis. Frey has seen in some cases better results than with other tuberculins. v. Holten, too, claims that tuberculol (tuberculol B, containing endotoxins) exhibits a greater power of assisting the healing of the pulmonary tubercular process than old tuberculin, bacillary emulsion or Béraneck's tuberculin. Its value was best seen in severe cases and after reaching the larger doses. Reactions could not be altogether avoided, but were quite harmless when once the higher doses were reached. We have ourselves employed the preparation in a large number of cases; it was not merely very well borne even where a tendency to severe hæmoptysis was present, but the patients showed a considerable retrogression in the anatomical signs of disease, were obviously better and increased considerably in weight.

### High Toxicity of Tuberculol.

The toxic power of tuberculol is much greater than that of old tuberculin. Patients immunized against old tuberculin still react to divisions of solution I of tuberculol. It is therefore a more difficult and lengthy matter to immunize against tuberculol. But we have not been able to prove by our prolonged experiments that it is superior in its curative effect to Koch's preparations.

Recently the two components of tuberculol, the toxins secreted into the culture medium and the extract of the bacterial bodies, have been separately manufactured. Landmann has also acceded to the request to prepare a tuberculol from bovine bacilli (Bovotuberculol).

## (7) THE TUBERCULIN PREPARATIONS OF KLEBS.

**Tuberculocidin.** A different line of thought from Koch's was followed by Klebs [176] in the production of his preparations. He believed that, besides the curative agent, a harmful toxin also was present in tuberculin, which he could split off by treatment with alcohol and bismuth. This was, then, the origin of his first preparation, to which he gave the name of tuberculocidin on account of the property he wished to attain—the destruction of the bacilli.



**Antiphthisin.** As his tuberculocidin was not yet quite pure, he prepared a second substance by precipitating the filtrate of a tubercle culture with sodium bismuth-iodide in acetic acid and absolute alcohol, and to this he gave the name of antiphthisin [177].

**Selenin.** Assuming, further, that every case of human tuberculosis is a mixed infection, he made a further improvement in his specific treatment by isolating a substance, which he called selenin, from the *Diplococcus semilunaris* (*catarrhalis* of Pfeiffer), which he himself discovered to be a frequent mixed infection, a solution of the bodies of the cocci with the toxins removed by  $H_2O_2$ . In severe cases another immunizing substance, tuberculo-protein, should also be used.

According to later publications [178], the indication is generally met by giving by the mouth 3 c.c. of tuberculocidin-selenin mixture twice a day. If abundant bacilli are present in the sputum larger doses of tuberculocidin added to the mixture are advisable.

**Tuberculo-sozin.** More recently still, Klebs recommended as a sequel to treatment with tuberculocidin-selenin, which should in all cases be employed first until the limit of its action is reached, his newest preparation, tuberculo-sozin [179], a substance obtained from dead tubercle bacilli by extraction with glycerine. To this substance he ascribes high immunizing and antipyretic properties. He now combines the use of these tuberculins with injections of tubercle bacilli from blind-worms (*cf.* pp. 197-198).

**Results.** Klebs has seen favourable results from his preparations both in animals and tubercular patients. Other observers have not confirmed this result, but agree in finding the preparations absolutely harmless. Petruschky's investigations with tuberculocidin in Koch's Institute gave a negative result; Langermann's were unfavourable. Better results were obtained by Gabrilowitsch, Longstreet, Taylor, Denison, F. A. Elsässer, Jessen and Pogue.

#### (8) BÉRANECK'S TUBERCULIN (TBk.).

By a process of his own, Béraneck [180] prepared a tuberculin which should contain as far as possible all the substances having immunizing properties whether in the culture fluid or in the bacteria themselves, but without the other toxins characteristic of some other tuberculins possessing no immunizing power and possibly even harmful.



### Preparation and Dosage.

It is composed of extracellular toxins of the broth culture of special formula and of intracellular toxins extracted from the protoplasm of the bodies of the bacilli with 1 per cent. phosphoric acid at a temperature of 60-70° C. It is prepared in fifteen different dilutions, the concentration of which rises in powers of 2 (not of 10, as with other tuberculins); each solution is therefore double the strength of the preceding one. The solutions are called A/<sub>128</sub>, A/<sub>64</sub>, A/<sub>32</sub>, A/<sub>16</sub>, A/<sub>8</sub>, A/<sub>4</sub>, A/<sub>2</sub>, A, B, C, D, E, F, G, and H. H is pure tuberculin. According to Sahli, the initial dose is usually  $\frac{1}{2}$  division of solution A/<sub>32</sub>. This dose is repeated two or three times. If a reaction should occur,  $\frac{1}{4}$  division of the solution A/<sub>32</sub> must be given, or the still weaker solutions A/<sub>64</sub>, A/<sub>128</sub> employed. Should no reaction occur, each injection is increased by  $\frac{1}{2}$  division up to a dose of 5 divisions of A/<sub>32</sub>, which is repeated several times. Then one passes to A/<sub>16</sub>, but of this solution, which is twice as strong, one only injects 1 division and then increases again by  $\frac{1}{2}$  division up to 5 divisions of A/<sub>16</sub>. This dose is also repeated several times, then 1 division of A/<sub>8</sub> is injected, rising by  $\frac{1}{2}$  division up to 5 divisions of A/<sub>8</sub>, and so on. As soon as the slightest reaction occurs the dose is reduced after it until the reaction has completely disappeared. Generally a slight reduction is sufficient to avoid reactions; it may, however, be necessary to begin the treatment again from the initial dose. Sahli gives the first injections twice a week, from about solution E once a week, and when the maximal dose is reached, only once every fourteen days. With good tolerance, the usual increase of dose may be 1 division; with susceptible patients it must be  $\frac{1}{4}$  division. In this way in favourable cases the maximum dose may be reached, which Sahli considers to be 10 divisions of the pure tuberculin solution H.

This tuberculin has been warmly recommended by Sahli, who has also used Koch's old and new tuberculin as well as Denys', and gives strong preference to Béranek's.

With regard to results, he states that certain cure may be reached in the slighter cases; often only a state of equilibrium between disease and organism is attained, a state of quiescence; in a third category of cases a degree of improvement is obtained, but such marked symptoms remain that even compensation of the tubercular process cannot rightly be claimed; the course of the disease remains progressive, but it has been prolonged.

**Clinical Results.** Besides Sahli, others have given a favourable opinion of Béranek's tuberculin, especially Pischinger, K. Bauer, Dluski, Frankfurter, E. Bauer, Kovács, and others; also Rollier, Pallard, Machard, and Mallet, in cases of internal and surgical tuberculosis. Less satisfied with its action is Amrein, who holds the tuberculins of Denys and Koch to be in every way superior, the old tuberculin of Koch vastly so.

From the existing literature Béranek's tuberculin appears to be preferred principally on account of its convenient method of application, a



purely external reason which should only apply where tuberculin is infrequently used.

And it must not be forgotten that solutions of tuberculin lose their efficacy the quicker, the more they are diluted and the longer they are kept. On this account we recommend the physician to make his own dilutions, a very simple matter. Moreover, nothing stands in the way of the other tuberculins being also diluted in the same progression by the user.

### (9) CARL SPENGLER'S TREATMENT WITH BOVINE TUBERCULIN.

Attention was first adequately called to the supposed superiority of the immunizing effect of bovine tuberculin on human tuberculosis by Carl Spengler [181]. His investigations were the result of Koch's teaching in regard to the specific difference between bacilli of human and bovine origin. Koch's own investigations had shown differences between the living cultures, not between their products of secretion and cell substances. Spengler wrote :—

#### Spengler's View of Relation between Human and Bovine Bacilli.

"The toxins of bovine tuberculosis are less toxic to tubercular man, far less than the tuberculins of human tubercle bacilli. As immunizing and curative agents they are far superior. The curative process in tuberculosis under their influence occurs in shorter time, and, because of their less poisonous character, safely and rapidly. My experiments with bovine toxins in man and those first of Koch and then of v. Behring relating to immunizing cattle with human tubercle bacilli, have established that there exists between the toxins of bovine and of human tubercle bacilli and their hosts a reciprocal antagonism of natural origin, in the sense of Jenner's discovery. The two originally identical infecting agents have become in their respective hosts alternating vaccines. The most striking result of the vaccinal qualities of the bovine toxins is that to tubercular man they are far less toxic than the human tuberculins, although the bovine bacilli show themselves more virulent to animals."

#### Origin of the Bovine Bacillus.

Carl Spengler takes up the dualistic standpoint of Koch. With his school he further assumes that a progressive infection cannot be produced in cattle with bacilli of human origin, nor in man with bovine bacilli; the latter contention he was himself the first to demonstrate by infecting himself with  $\frac{1}{2}$  mg. of living bovine bacilli.

His view, however, is that the bovine bacillus originated from man, a view in part supported by Kitasato's researches on bovine tuberculosis in Japan, confirmed by Deycke for Turkey. He holds the bovine bacillus to be a variety, adapted to its bovine host, of a bacillus living in symbiosis with the human tubercle bacillus. He named this differentiated bacillus *Perlsucht* and later *Bacillus humano-longus*.



**Occurrence of  
the various  
Forms.**

According to his bacteriological researches [182], the *Bacillus humano-longus* in the majority of cases lives in symbiosis with the short tubercle bacillus. A smaller percentage rests on a pure tubercle bacillus infection, and in these the prognosis is bad. Rarest are the cases in which the *humano-longus* type is found almost alone, and these have a more favourable character. The unadapted genuine bovine bacillus is harmless to man; it may be pathogenic to the tubercular subject, but in this case is certainly of low virulence.

Schroeder [183], in the sputum of 100 cases, only found eleven in which bovine bacilli in Spengler's sense were present. In ten cases the sputum was almost non-toxic in rabbits. The inoculation of the eleventh sputum only was always followed by a severe, fatal form of tuberculosis but proved without danger for cattle [184]. In contradistinction to Carl Spengler, all cases which showed in the sputum the characteristic bovine bacilli belonged to the forms of human phthisis of bad prognosis.

**Application  
to Tuberculin  
Therapy.**

These studies led Spengler to develop his method of individual tuberculin therapy in accordance with the etiological factor [185]. The toxins of the human and the bovine bacilli have, like the bacilli themselves, an antagonistic action. For tuberculin treatment that preparation must first be chosen which has not a highly toxic action and which least depresses the general health. This substance is the vaccine and originates from that variety of bacillus which is not predominant in the disease. Only later on, after a preliminary immunizing course with the vaccine, is the employment of the toxin proper admissible and then generally advantageous.

**Bacilli shewn  
Different by the  
Precipitin Test.**

Confirmation of Carl Spengler's dualistic theory of infection has been given by Bonome [186], who succeeded in showing a tangible difference between the bovine and human bacilli by means of the precipitin method. According to his results, organic extracts of human tuberculosis are always agglutinated in respect of either micro-organism, whilst the extracts of bovine tuberculosis give neither plural agglutination nor plural precipitation. Cultures of human bacilli injected into cattle give little or no bovine agglutination, but a very marked one when injected into man. From these sero-diagnostic results Carl Spengler draws the conclusion that human tuberculosis cannot be of bovine origin, but is propagated from man to man as a double infection. Bovine tuberculosis originates, like all other infections of domestic animals, from man; the bovine bacilli are a variety of the symbiotic *Bacillus humano-longus* of man. In this direction also Koch's dualistic conception receives confirmation.



**Carl Spengler's  
Immunizing  
Substances.**

Carl Spengler's immunizing substances are as follows: ATO (*Alt-tuberkulin-original* = original old tuberculin) consists of the non-concentrated culture fluid of tubercle bacilli of human origin freed from bacilli by filtration. 1 c.c. corresponds to 0.1 c.c. of old tuberculin. Initial dose, '00001 to '0001 c.mm. Maximal dose according to the case. Absolute maximum 1,000 c.mm.

Vacuum tuberculin is ATO concentrated to one-tenth of its volume at a low temperature under reduced pressure: 1 c.c. corresponds to 10 c.c. ATO or 1 c.c. of old tuberculin.

PTO (*Perlsucht-tuberkulin-original* = original bovine tuberculin) is prepared from bovine bacilli in an analogous way to ATO. 1 c.c. PTO corresponds to 0.1 c.c. bovine old tuberculin. Initial dose '00001 to '0001 c.mm. Maximal dose according to the case. Absolute maximum, 1,000 c.mm.

Bovine vacuum tuberculin is PTO concentrated to one-tenth of its volume at a low temperature under reduced pressure. 1 c.c. corresponds to 10 c.c. PTO or 1 c.c. of old tuberculin.

These four preparations of Carl Spengler's are also supplied by the Farbwerke Hoechst without attaching his name to the products (*cf.* pp. 163 and 164).

Tubercle bacillary emulsion (TBE) and bovine bacillary emulsion (PE) correspond in method of preparation to those of Koch.

To supply the demand for substances producing a toxic and bacterial immunity based on the antagonistic working of the two components in the dualistic etiology of tuberculosis, Carl Spengler originated vaccines, about the composition of which nothing is yet exactly known.

PV (bovine bacillary vaccine) is the antagonist of TBV (tubercle bacillary vaccine).

Initial dose '000000001 to '00000001 c.mm. Maximal dose, according to the case, *i.e.*, the dose which leaves behind a swelling slow of absorption at the site of injection, avoiding one which produces abscess, or a dose which acts toxically, rendering necessary the application of the antagonist.

TBV (tubercle bacillary vaccine) is the antagonist of PV (bovine bacillary vaccine).

Application as under PV. Doses may be injected every day or with longer pauses according to the case. As a rule the lower doses are increased each time tenfold, the higher doubled.

If the immunizing substance be not well borne and produces toxic



reactions, *e.g.* deterioration of health, acceleration of the pulse, marked increase in the quantity of sputum, cough, rise of temperature, &c., the antagonist must be injected. The smallest dose is given to start with, and on increasing it the toxic action of the vaccine first used is abolished.

**Clinical Results.** Favourable results with the preparations of Carl Spengler are recorded in recent literature by various observers; thus by von Brauns, Frühwald, Hollós, and others. v. Szabóky [187], who has made a thorough study of Carl Spengler's method and all investigations pertaining thereto for a long time, is, however, very reserved in his opinion.

Moreover, the general opinion is that the differences in the tinctorial and morphological condition of the tubercle bacilli in the sputum only point to the amount of variety between the tubercle bacilli of the *typus humanus*. In the same way the antagonistic reactions to the preparations of human and bovine origin, which were supposed to enable a conclusion to be formed as to the etiology of the exciting cause, have hitherto found no acceptance.

**Bovine  
Tuberculins of  
Lower Toxicity.**

We ourselves have used bovine tuberculins (p. 164) and bovine bacillary emulsion (p. 173) from the Koch Institute in a large number of cases and have proved that the lower toxicity of the bovine old tuberculin, as compared with tuberculin made from human bacilli, is absent in the emulsions made from the two kinds of bacilli. The idea, therefore, occurs that the lower toxicity is due to the culture broth possessing fewer toxins of the bovine bacilli, owing to their poorer development in culture medium used, which is more favourable to the growth of human than bovine bacilli. The difference, then, in toxicity would be quantitative only and not qualitative.

**Ruppel's  
Experiments.**

According to Ruppel's [172] investigations, chemical analysis of many bovine stocks has shown qualitatively the same products of the bacillary body as were found in the bacillus of human type. Not much importance can be attached to quantitative differences in these investigations, as the quantitative proportions of the various substances may be subjected to relatively severe fluctuations in different stocks of the same kind of tubercle bacilli. In his experiments on animals, Ruppel was unable to prove any difference in action between the two forms of tuberculin.

**Conclusions.**

In consideration of the contradictory results of the investigations made up to the present as to the difference between the tuberculins prepared from human and bovine bacilli (R. Koch, Penrose, C. Spengler, Kanda, de Jong, Wolback and Ernst, Ruppel, Bandelier), Weber and



Dieterlen [188] have worked in the Sanitary Board with tuberculins of equal titre. They found our supposition confirmed that the difference in the toxicity of the two tuberculins is in fact only quantitative. Experiments on cattle and guinea-pigs gave similar results in the diagnostic use of tuberculins of equal titre.

#### (10) OTHER TUBERCULINS ON THE LINES OF KOCH.

##### **Basis of various other Tuberculins.**

The ideas underlying the preparation by various workers of tuberculins on Koch's lines tend, in the main, in two directions. On the one hand, the protean course of tuberculosis was explained not only by the varying "culture medium" of the tubercular individual, but a definite significance was ascribed to the tubercle bacillus of the individual case. Then Koch's old tuberculin, in addition to the secretions of the living bacilli, their metabolic products and portions of the cell bodies set free during their natural destruction and by extraction during the concentration of the culture broth, also contains other substances derived from the culture medium which are unimportant as far as the specific action of the tuberculin is concerned (extractive substances from the meat, peptone, &c.). Other investigators have considered these non-specific substances to be less inert than Koch and have sought to eliminate them by various chemical methods. Working on both these lines, various other tuberculins have been prepared besides those already described, but all based on Koch's principles.

##### **Tuberculin from Patients' own Bacilli: Specific Tuberculin.**

Starting from the assumption that the varied course of tuberculosis is not sufficiently explained by the difference in the "soil" of the tubercular individual, a view supported by the observation that apparently the most similar cases behave widely differently in their relation to specific treatment, Krause [189] laid emphasis on the fact that the tubercle bacillus itself here plays the principal rôle, the more so as cultures of equal virulence on the same medium may develop quite differently under the same experimental conditions. Hence he believes that every tubercular subject houses his own disease-producer and that treatment must be conducted with tuberculin produced from the patient's own bacilli, and for this purpose he prefers a specific bacillary emulsion. This is also the opinion of Hüntjens and Rothschild; the latter bases his verdict on opsonic tests on patients so treated. Priority, however, really belongs to Löwenstein [190], who,



in 1905, made the claim for the "ideal specificity" and placed it on an experimental foundation; he recommends "that tubercular patients be treated with tubercle bacilli grown from the case in question, or with active preparations derived from them." Krause gives detailed notes of several cases successfully treated thus, but himself demands a strict scientific repetition on larger clinical material.

Apart from the fact that such a method is impracticable on a large scale, it seems to us further not well grounded in theory. And the cases cited do not seem designed to prove its superior value.

**Rothschild's  
Mixed  
Tuberculin.**

The same may be said of the Auto-Tuberculin of Rothschild [191], based on the same conception. He does not recognize any difference in principle between the numerous tuberculins, and considers his treatment with auto-tuberculin to be the ideal form of application. But as this procedure now seems to him impracticable on account of its practical difficulties, he thinks he has found a solution of the problem in his mixed tuberculin. It is a mixed tuberculin composed of as many varieties as possible of the *typus humanus*, a polygenous bacillary emulsion. He assumed that in this way it was extremely probable that specific protective bodies would be formed against that variety of tubercle bacilli from which the patient happened to be suffering. Out of eighty-two cases of tuberculosis, some of which were serious, he cured forty-seven. In laryngeal tuberculosis, too, this modification of the bacillary emulsion has proved efficacious.

F. Rosenfeld, in an excellent treatise [192], in which he declares himself to be a convinced believer in tuberculin, tells us that he has treated twenty-five cases, some of which were exceptionally difficult, with good results with this mixed tuberculin. He does not assert, however, that the same results could not have been attained with Koch's bacillary emulsion.

**Wolff-Eisner's  
Mixed Tuberculin  
(T + TR).**

Wolff-Eisner recommends a combination of old and new tuberculin, made according to his directions, and which he calls "Mixed Tuberculin," a name already chosen by Rothschild for his polygenous bacillary emulsion. Wolff-Eisner considers this combination a very simple but satisfactory solution of the complex question, of which preparation is the most appropriate for tuberculin treatment. Information as to the results of the use of this mixture is not to hand, but only persistent claims for its value.



We consider this combination very simple but not a happy one. Many patients tolerate old tuberculin better than bacillary emulsion; with others the reverse is the case. Susceptibility to one part of the preparation may prevent immunization against the other substances it contains. Such observations have already been made by Jochmann. The obvious endeavour to immunize to as many substances in the tubercle bacilli as possible led us (and after us Koch and Jochmann) in cases which were very susceptible to the bacillary emulsion to treat first with old tuberculin preparations, after which immunization to the former was much more quickly achieved.

**Denys' Tuberculin;** Denys [193] filtered tubercle cultures through porcelain and avoided boiling the filtrate, assuming that useful toxins were thereby destroyed.

**Based on Animal Experiment.** Denys' tuberculin then contains, besides toxins secreted by the living bacilli, only those proteids from the dead bacteria which go into solution in the culture fluid, whilst the insoluble proteids which remain in the bacterial bodies do not come into action. Denys injected healthy dogs with his tuberculin in increasing doses, with the result that a subsequent infection with a lethal dose of tubercle bacilli produced no signs of disease. On treating dogs which had previously been infected some survived, and in others a distinct inhibiting influence on the disease could be noted, and some retrogression of the morbid changes in comparison with control animals. Also goats previously treated with Denys' tuberculin stood a subsequent infection with living tubercle bacilli without harm.

The animal experiments seem somewhat scanty, a fact which Denys justifies on the ground of expense and because analogous action in the tubercular human subject does not necessarily follow.

He then employed his preparation with good result on man. His own experience extends over more than 2,000 cases which he has treated himself or indirectly through other practitioners.

**Principles of Dosage.** The principle of Denys' treatment is the mildest form of administration, avoiding all marked reaction, in which term he includes not merely fever but other general disturbances. He considers febrile reaction not merely unnecessary, but an actual hindrance to the occurrence of immunity as well as dangerous for the patient. The maximal dose is determined according to individual tolerance. In contrast to Petruschky's interrupted method of treatment, he considers it necessary to keep up the tox-immunity for as long as possible in order to give the organism time for the healing processes. During treatment, pulse and body-weight are specially to be considered; fever is no contra-indication.



We have already pointed out that Denys' tuberculin is nothing else but Koch's non-concentrated tuberculin, his original tuberculin. In consequence of its wide use on the Continent, it is now also prepared in Germany. In speaking of original tuberculin (TOA) we have already said that we cannot demonstrate any superiority of this preparation to Koch's old tuberculin. Moreover, a critical examination of the literature available (for example, that of Schnöller, P. C. F. Koch, Amrein, Kersbergen) can lead to no other conclusion.

#### **Gabrilowitsch's Endotin.**

Gabrilowitsch's endotin, according to his experiments on animals, is supposed to possess all the valuable specific qualities of Koch's old tuberculin without causing violent reactions.

#### **Preparation.**

It is made in a similar manner to Koch's preparation from tubercle bacilli of the *typus humanus*. After previous treatment with alcohol, xylol, ether and chloroform, followed by decanting and centrifugal processes, it is finally treated with hot, diluted lye, to separate the by-products contained in old tuberculin (fats, carbohydrates and albumen) which cause general reactions, but have no curative effect. High fever is supposed to be no contra-indication as it is to Koch's old tuberculin. Initial dose, 0.01 c.mm.; maximum dose, 200 c.mm.

#### **Conflicting Estimates of its Value.**

Gabrilowitsch [194] reports good results and describes the preparation as a powerful remedy for tuberculosis. In a treatise emanating from his sanatorium, Kurdjumoff has recently recommended it for the treatment of latent tuberculosis and phthisis incipiens of children over 10 years of age. As objective improvements he cites a favourable influence on raised temperature and on tubercular glands in the neck. The efficacy of the preparation is confirmed by Bandevin, Blumenau, Böhm, Deal, Gordon, Helms, Hirschberg, Iwanow, Lapschin, Masing, Michailowa, Rostoschinsky, Slatowerkownikow. W. Neumann prefers it to all other tuberculins. Horol, Gaikowitsch, and Vos have not observed any superiority to Koch's tuberculins. According to Curschmann's and Walterhöfer's observations on twenty-five patients, not only was there no good effect whatever, but in many cases the condition of the lung changed for the worse. Gordon [195] tried with much emphasis, but not with convincing logic, to prove to the Scientific Congress in Königsberg in 1910 that endotin was the one and only active substance of tuberculin. He overestimates the quantity of non-specific substances which are supposed to be injurious in Koch's old tuberculin, which are, it is true, not absolutely indifferent, but need not be considered on account of their small quantity. Moreover, old tuberculin produces no toxic symptoms when used in high dilutions. The difference between endotin and old tuberculin is presumably quantitative, not qualitative. Gordon's attempt to explain the febrile reaction caused by the tuberculins hitherto used as the effect of albumose is quite a mistake and long ago refuted.

Landmann remarked in the discussion at the above lecture that it was



impossible from a chemical point of view to remove the albumose from the tuberculin according to the methods described; he considers its separation generally impossible. Gordon's published results are very good; but no such enthusiastic verdict has been received up to the present from any other quarter, not even from Gabrilowitsch himself. And in reference to the assertion that endotin never produces fever, and that fever in cases of advanced phthisis is no contra-indication, it must be mentioned that according to Masing all Russian physicians who have had much experience with endotin cease the treatment when the evening temperature exceeds  $38.5^{\circ}\text{C}$ .

Also, according to the scanty information of recent German literature, endotin produces febrile reactions even with cautious dosage, so that it does not deserve to be described as pure or non-toxic tuberculin. The problem of how to isolate and purify the specific substance from the tubercle bacilli for purpose of immunization is as yet unsolved, although it has been ceaselessly studied ever since the discovery of tuberculin. According to Jochmann's and Möller's investigations, endotin is certainly free from albuminous substances, but at the same time the specific substance is considerably injured, as even 100 c.mm. of endotin is not sufficient to kill a tubercular guinea-pig (in contrast to the fatal dose of 5-10 c.mm. of old tuberculin), and because the preparation in the concentration on the market contains no substances which can be proved either by fixation of complement or by the precipitin method to have a specific action.

Also, according to Hinze's experiments, endotin contains but very small quantities of tuberculin, for only in the most sensitive patients could he obtain a positive cutaneous reaction with the strongest solutions, and this even was much less severe than that obtained with the higher dilutions of old tuberculin.

Endotin is therefore not a progressive step in specific treatment and has nothing in common with Koch's albumose-free tuberculin, except the absence of albumose.

**Calmette's Tuberculin (CL).** Calmette brings an article into the market under the name of Tuberculin CL, which he considers essentially different from the tuberculins hitherto produced in action, strength, and effect. The points of difference and advantage lie in the strong concentration, the slight toxicity and the striking fact that fever never occurs and the rise of the opsonic index shows the curative result. Little is known as to the efficacy of the preparation from other quarters. Ribera y Sans tried it in six cases of tuberculosis of the joints, and not only noticed no improvement in the local infection, but a most unfavourable effect on the general health.

**Composition and Dosage.** Tuberculin CL is supposed to contain all the secretions produced by the tubercle bacilli in the cultures, as well as the protoplasmic substance of the bacillary bodies extracted *in vacuo* by means of glycerine, capable of precipitation in the cold by absolute alcohol, not capable of dialysis by ether, soluble in normal saline. It is supposed to be ten times stronger than the preparation which is precipitated by alcohol



from cultures of tubercle bacilli sterilized by heat and a thousand times stronger than Koch's old tuberculin containing glycerine. Its strength is ascertained by the determination of the lethal dose by intercerebral injection in healthy guinea-pigs; this dose amounts to 8-10 c.mm., in contrast to 8 c.c. of old tuberculin. It is injected in increasing doses of 0.0001 to 1 c.mm. at intervals of twelve days for a long time; generally twenty-four injections are required to complete a cure. But it must be pointed out that intercerebral injection as a test for toxicity, also used by v. Lingelsheim, has been already abandoned in Germany because it offers too little guarantee for the specificity of the effect. So that according to Koch the test of tubercular toxins on healthy animals must be rejected as unsuitable, because it cannot serve as a measure for the quantity of specific substance contained in a preparation; for it is just the peculiar characteristic of the tubercular toxin that it exhibits its toxic action only in a tubercular and not in a sound organism. Moreover, in testing tuberculins it must be proved that the preparation possesses the power of producing in the tubercular organism the anatomical changes which are typical of a tuberculin reaction (Ruppel).

**Rosenbach's  
Trichophyton  
Tuberculin.**

The latest modification of tuberculin is Rosenbach's tuberculin [196], of which Rosenbach says that it arises through biochemical processes in the growth on living tubercle bacilli and their culture medium of a hyphomycete which flourishes in living human and animal tissue. This is the *Trichophyton holosericum album* first described by him.

The trichophyton, according to Rosenbach, is easily developed in cultures of tubercle bacilli. It grows luxuriantly in the culture in large patches, partly as threads, partly as a widespread network. After the trichophyton has grown for some time the tubercle bacilli, according to Rosenbach, show modifications plain to the naked eye, which are betrayed by a darker colour and decay of the zooglœa, and under the microscope are clearly seen as involution forms of the bacilli. The changes brought about in the culture medium by the trichophyton fungus were not only on the surface but throughout the culture. Rosenbach supposes that the whole of the tubercle bacilli culture is affected by the fungus in such a way that the toxic, less stable molecular body is changed or destroyed, whilst the more stable, immunizing, antitoxin-forming elements remain.

**Preparation.**

Rosenbach prepares the tuberculin in the following way:—

Particles of the trichophyton fungus are added to cultures of tubercle bacilli from six to eight weeks old. At a temperature of 20-22° C. this fungus develops, and after ten to twelve days has covered the greater part of the culture of tubercle bacilli with a white mycelium. Then the mass (tubercle bacilli and fungus culture) is separated from the culture medium, mixed with a solution of glycerine and carbolic acid, ground, filtered and added to the filtered culture-fluid. The volume is increased to just ten times that of the original culture-mass (tubercle bacilli and trichophyton), and to preserve the tuberculin an addition is made of  $\frac{1}{2}$  per cent. of carbolic acid.



**Use in Surgical  
Tuberculosis ;**

**Locally :**

In surgical tuberculosis it is employed locally and subcutaneously. Local injection assures energetic action of the tuberculin, and is preferable in all cases where it is practicable. In closed foci it should be injected as near the centre of the foci as possible, where there is a tubercular space. In open foci, the injection of the tuberculin into the tubercular spaces and fistulæ only results in focal and general reaction without perceptible healing action ; the latter is only observed after injection into the walls and floor of the focus, but care must be taken that it does not escape and become useless by means of the granulation or fistulæ. The various surgical measures, such as incision, drainage, dressing, rest, or movement of joints, &c., must be observed.

**Subcutaneously.**

The subcutaneous method is limited to cases of surgical tuberculosis, where the foci cannot be reached by local injection (tuberculosis of the vertebræ, inaccessible glands, peritoneum, &c.). Its action used thus is not so striking. The curative action is certainly not to be underestimated and is lasting in the case of closed foci (*e.g.*, tuberculosis of vertebræ), but it is more or less ineffective in the open forms, especially if there are secondary causes of suppuration. The subcutaneous method is also the only one applicable to pulmonary tuberculosis.

**Value  
of Reaction.**

Rosenbach emphasizes that a focal and general reaction is necessary if the tuberculin is to be effective ; it should reach a considerable but not extreme degree. He states that he has never observed harmful effects nor the formation of new foci as a result of the reactions, which are both of curative value and absolutely essential. Non-tubercular individuals tolerate the tuberculin, according to his experiments, in fairly large doses without disturbance of the general well-being. It can also be employed in diagnosis ; reaction is evident as infiltration at the place of injection and subsequent rise of temperature. Rosenbach gives the following technique for the injections :—

**Rosenbach's  
Method.**

In therapy the injection of the tuberculin should be made into the focus itself in all cases where this is possible. Subcutaneous injection may be indicated alone or in addition to local employment, where other tubercular affections are present inaccessible to the local method, or also at the commencement of treatment in order that the reaction to the first injections into the tissue itself may be milder. The initial dose subcutaneously was almost always 200 c.mm., even with the smallest children. Only where a test injection showed special susceptibility was the dose correspondingly reduced. This dose was raised in the subsequent injections,



generally by 100 c.mm. each time, but in many cases not so frequently, and sometimes a smaller increase was made according to the reactions and condition of the patient. The interval between the injections was chiefly governed by the reaction, also by the condition of the patient and size of dose. Small doses without perceptible reaction were, since they were too small, often repeated on the following day, those with considerable reaction in three to seven days and those with very severe reaction in eight to ten days. Particularly with the larger doses towards the end of treatment, a pause of fourteen days was often necessary. In addition to the cessation of the reaction, nutrition is often to be considered in determining the time of repetition, for the appetite may be considerably reduced in moderate reactions for one or two days, in severe reactions longer. When no reactions occur to the higher doses the treatment is finished.

### A Case of Weakened Tuber- culin Action.

Judging by the histories of the patients, we hold that the results do not prove a superior healing action to that of the most used tuberculins. Considered impartially, one gets the impression from the cases treated subcutaneously that it is a case of *weakened* tuberculin action. The intrafocal treatment in suitable cases of surgical tuberculosis of glands and lupus is more individual, though the principle is not new. This method of treatment with proved successes in a large number of cases is possibly the most important part of Rosenbach's experiments; the method was, however, previously used by Lenzmann in surgical tuberculosis (*cf.* p. 266), who used old tuberculin. We are inclined to attribute these successful results not to Rosenbach's tuberculin, but to the method. The latter is, indeed, not a new one, but had been practised for many years in lupus with Koch's tuberculin (*cf.* p. 259); and the effect was exactly similar to that observed by Rosenbach. We repeat that the results published, both local and general, give the impression of weakened tuberculin action, which would only be expected considering the mode of preparation of the tuberculin. There seems to be no sufficient proof of a specific bio-chemical influence of the trichophyton fungus on the tuberculin.

### Experiences with Rosenbach's Tuberculin.

Seyberth has treated ten cases of localized tuberculosis with this tuberculin, of which eight were much improved locally and generally. H. Curschmann's successes in pulmonary tuberculosis of various stadia were very encouraging. A case of tubercular periostitis, which was treated not with local but intramuscular injections, showed clinical cure in five weeks; a case of caries of the metatarsal bones was not influenced. On the ground of further experiences, he recommends the preparation also for children and particularly for febrile patients, as he considers its antipyretic action and the improvement of local symptoms in cases of favourable prognosis quite apparent and very prompt. He emphasizes the relative insignificance of the focal reactions.



According to experiences in the First Medical Clinic in Berlin, published by Köhler and Plaut [197], the tuberculin is to be regarded as an active remedy for pulmonary tuberculosis. Of thirty-four cases, 85.4 per cent. had a positive result; the objective pulmonary symptoms disappeared in 41.2 per cent. and also increase of weight, disappearance of fever and improvement of the subjective symptoms were observed. These results were obtained not only with patients in the first stadium but also with many in the second, chiefly, however, with slight cases.

Still more favourable are the results of Stolzenburg [198] in a series of twenty severe cases. Two tolerated the preparation as badly as other tuberculins. In one the result was practically *nil*, in two but slight. Fifteen showed very considerable objective improvement; ten lost the bacilli from the sputum.

Schaefer [199], on the contrary, observed no special action of the preparation in thirty-four pulmonary cases, of which two also had surgical tuberculosis; he obtained the impression that by the action of the trichophyton the tuberculin had entirely lost its specific character. He was also always unsuccessful in producing a positive cutaneous reaction with the preparation.

Koch, also, never obtained success with it.

### Iron Tuberculin.

Ditthorn and Schultz [200 and 201], from old tuberculin, from watery extracts of washed bacilli arising in old tuberculin cultures, from fresh tubercle bacilli or bacilli freed from fat, also from culture fluids separated from bacilli, obtained precipitates with basic iron chloride; these, after removal of the chlorine and albumin by washing with sterile water, gave clear solutions in very dilute caustic soda. These iron tuberculins (which contain considerably less non-specific but not indifferent albuminous substances than old tuberculin) have proved of utility in their diagnostic and therapeutic experiments; general toxic symptoms were, as a rule, considerably reduced, and in many cases great local improvement was seen.

### Reports.

According to Schellenberg [63] "iron tuberculin A" prepared from old tuberculin bears a close relation in action and usefulness to the albumose-free preparation: general and febrile reactions are less frequent and milder than with old tuberculin; the larger, more active doses can be relatively quickly reached without severe febrile reactions; the clinical results are good and are not inferior to those obtained with other preparations; iron-tuberculin is especially suited for ambulant treatment on account of the very slight accompanying symptoms.

Amrein [202] finds that iron tuberculin A is better borne than old tuberculin and permits of quicker rise to large doses, but is less valuable as regards therapeutic activity. In the cases unsuccessfully treated, aggravation of the condition was not observed. Amrein recommends it for cases which need special caution in tuberculin treatment.



**Iodized  
Tuberculin.**

Cantani [203] observed an antiseptic action of iodine on tubercle bacilli and also believes in its antitoxic action in tuberculosis. He is of opinion that the internal application of iodine neutralizes the febrile action of tuberculin, without affecting its specific properties. He has therefore rendered cultures of tubercle bacilli non-toxic by means of iodine and has prepared an iodized tuberculin which produces no febrile reaction.

Marchesini and Pende have made experiments in guinea-pigs infected with tuberculosis, using a combination of old tuberculin and iodine ("Sierosin" prepared by Sbarigia), and found that in the lungs, glands, spleen and liver the most varying degrees of fresh formation of connective tissue could be recognized; especially in glandular tuberculosis, complete anatomical healing was observed.

Turmann [204] has had a preparation similar to Cantani's made by Merck and Co.

It is supposed to be a chemical combination of iodine and the albuminous substances of tubercle bacilli and to have a favourable action on experimental tuberculosis in animals. This recalls the work of Leonardo in the Duranto Clinic at Rome; he sought to explain the favourable action of iodine on the tubercular process by the fact that the iodine treatment raised the opsonic index. Iodine is retained in tubercular foci for about four days, whereas in other inflamed foci it is no longer demonstrable after twenty-four hours. By this means a number of leucocytes and an increased quantity of protective substances are found.

**Arsenical  
Tuberculin.**

Owing to the very favourable experiences of Benario with regard to the increased curative effect of new tuberculin bacillary emulsion when accompanied by subcutaneous injections of sodium arsenate (Fowler's solution), the Hoechst Farbwerke have produced an arsenical bacillary emulsion. For this purpose they bred tubercle bacilli of the *typus humanus* on culture fluids containing arsenic, and by gradual systematic increase in the additions of arsenic finally produced tubercle bacilli "immune" to it; these grew luxuriantly on culture media with a considerable arsenic content and moreover during their growth absorbed with their bodies some considerable quantity of it. Chemical analysis of these tubercle bacilli has shown that they contain 0.3 per cent. of arsenic (corresponding to about 0.6 per cent. of arsenious acid). For a year we used the arsenical bacillary emulsion along with the ordinary bacillary emulsion, in 200 cases without seeing any obvious superiority of the one over the other. The injections are borne without reaction.



**Molliment.** New preparations have been made by treating tubercle bacilli with soap and various oleates. Noguchi [205] has discovered that soap is very injurious to certain bacteria.

With the idea that the wax sheaths of the tubercle bacilli must be much better permeated by soap than by other watery agents, he tested its bacteriolytic power on them. He not only succeeded in completely killing them, but he was also able by previous treatment with tubercle bacilli which had been killed with Venetian soap to immunize guinea-pigs against infection with a virulent culture of the same stock. Independently of Noguchi, Zeuner [206] obtained, by treatment of cultures of tubercle bacilli with a solution of Venetian soap, an extract containing both the fatty and wax substances and the protein of the bacillary bodies which exercises a distinctly immunizing influence on tuberculosis in guinea-pigs.

**Zeuner's Method of Preparation.** For the treatment of human tuberculosis, Zeuner makes the preparation as follows: He extracts and saponifies a culture of tubercle bacilli with sodium oleate for many days at a constant temperature of 37° C., shaking the mixture continuously, and then heats it to 70° to 73° C., so as completely to kill all bacilli and to break down the wax-sheaths. This filtrate, first called "Prosperol," then "Tebesapin," is now designated "Molliment" (Preparation No. 8).

**Experiments with Molliment.** Attempts to immunize calves, which tolerate both intravenous injections of the filtrate and also of the saponified bacillary bodies, took a favourable course and promised good results (Zeuner and Broll). Even guinea-pigs so treated lived longer than the control animals. Recent investigations by Marxer [207] also show that sodium oleate can kill tubercle bacilli and by the use of bacillary emulsion treated with it, immunizing and beneficial effects on the course of the disease can be obtained in guinea-pigs; goats previously treated with it are rendered resistant to a severe artificial infection or even completely protected against it by suitable experimental treatment.

Citron and Munk were unable to promote the formation of antibodies by treating healthy guinea-pigs with the preparation; nor could they obtain a satisfactory immunization. But the average duration of life of most of the treated animals was somewhat longer than that of the control animals, and the course of the disease as regards the spreading of symptoms was in many cases considerably more favourable.

**Method of Use and Results.** In the treatment of human tuberculosis, Zeuner [208] has abandoned the original subcutaneous method on account of the painfulness of the injections. He administers it by mouth in the form of keratinized pills, soluble in the small intestine, and in hardened gelatine capsules (three, one to three times a day) or *per rectum* ( $\frac{1}{4}$ ,  $\frac{1}{2}$  and 1 c.c. in two concentrations



every second or third day). Senator, Citron and Masskow's results show that the remedy is well borne. Jessen states that it has without question an immunizing action. Bergell has obtained satisfactory results, and the recent experiences of the Berlin charities are also favourable. Weicker claims good results even in severe cases.

**Haentjens' Filtrase.** Haentjens [209] endeavoured to obtain from the tubercle bacilli, without injury to the bacillary bodies, their normally secreted toxin by imitating the natural processes in the tubercular organism.

**Preparation.** Experiments on animals with filter-candles containing enclosed tubercle bacilli show that the toxins diffused through the candles exactly resemble those which are emitted from the natural tissue-wall of the tubercle. As these toxins are also produced *in vitro* when the filter-candles are placed in a flask with distilled water, Haentjens makes use of the following procedure to obtain them. Tubercle bacilli from three to five weeks old, grown on glycerine-potato or Hesse culture medium, are put into the filter-candles with an equal quantity of powdered salt, so that after the interchange of salt and water in the candles and flasks normal saline is produced; the tubercle bacilli continue to live in this, and are supposed during their stay of fourteen to thirty days in the incubator at a temperature of 37° C. to separate their toxins.

Haentjens describes this preparation, which he calls "Filtrase," as a genuine endotoxin arising from the bodies of the bacilli themselves.

**Auto-antigens.** Similar experiments to treat tuberculosis with a filtrate obtained from the patients' own sputum, which might be termed an auto-antigen, have lately been made by Ruhemann, Passini and Wittgenstein, Hoffmann and Martin, and Roswell Pettit, apparently independent of one another.

Ruhemann, in particular, claims to have observed a favourable influence of this sputum filtrate on advanced phthisis. He has also used sputum extract in other cases—of tuberculosis of the skin, choroid and bladder—and states that the case of tuberculosis of the bladder was thereby cured.

**Tuberculoplasmin.** Buchner and Hahn's [210] Tuberculo-plasmin is very like Koch's new tuberculin. The preparation is obtained by grinding moist tubercle bacilli with quartz dust and crushing under high pressure. The



investigators obtained good results in experiments on animals. Möller failed to obtain them in men.

**Tuberculomucin.** Weleminsky [211] succeeded, by a culture method of his own, in changing a stock of tubercle bacilli in eight years to such an extent that amongst the products of metabolism, coagulable albumin and particularly mucin were produced. The broth, containing mucin and freed from bacilli by filtration through paper and sterilized by addition of phenol, exhibited a considerably greater immunizing power in experiments on tubercular rabbits and guinea-pigs than ordinary cultures, and this increased from generation to generation. The active principle of tuberculomucin he holds to be something other than the tuberculin doubtless contained in it, from which it differs chemically and clinically. According to the only reports at present published—those of Pachner [212]—it has proved satisfactory in internal and external tuberculosis.

Pachner with this preparation has treated thirty-five cases of pulmonary tuberculosis of varying severity (in unfavourable hygienic conditions practically without subsidiary measures) in ambulant practice with the result that ten were cured, eighteen restored to working capacity, six distinctly improved and able to work to a certain extent. There is no exact statement as to its influence on the sputum and its content of bacilli.

Further, two cases of tuberculosis of the skin and two cases of caries of the ribs with fistulæ, one complicated with glandular abscesses, were cured; one case of tuberculosis of the iris, ciliary body and cornea was much improved.

**Other Tuberculins.** Little is known of the employment and clinical results of other tuberculins. These are chiefly unimportant modifications of Koch's preparations and include the tuberculins of Hirschfelder, Jessen, Maréchal, Jacobs, Baudran, and Sciallero.

Other authors have attempted to prepare an active and less toxic preparation by growing the tubercle bacilli on other culture-media: *e.g.*, Vesely by growth on glycerine; Maksutow used a similar method; de Schweinitz added phosphates to the culture-fluid.

The same object has prompted experiments in preparing tuberculin on Koch's principles from bovine bacilli (Carl Spengler), avian bacilli (Roux), blind-worm bacilli (Möller), piscine bacilli (Ramont and Ravaut), and from various acid-fast organisms. No practical results have been seen from these various experiments.



## (11) ACTIVE METHODS OF IMMUNIZATION ON THE LINES OF JENNER AND PASTEUR.

Besides the active immunization by means of bacterial cell substances, an attempt has many times been made to reach the same end with living and dead bacilli themselves. In giving a short *résumé* of what has been done in this sphere of work, we shall show the direction in which previous research has been tending and in which, to all appearances, successful inoculation against tuberculosis of man seems to lie within attainable distance.

**Immunization  
with Attenuated  
Cultures ;**

On the analogy of vaccination in small-pox, the attempt was made to produce a form of light curable tuberculosis by means of attenuated cultures and so immunize against the more severe form. The names need only be mentioned of Auclair, Falk, Grancher, Masentow, Héricourt and Richet, Péron, Paterson and Tommasoli. Following on Pasteur's lines, the cultures to be injected were attenuated by putrefaction, heat or antiseptics; all with negative result. Cavagnis recorded favourable results of immunization in guinea-pigs and rabbits by inoculating tuberculous sputum, previously treated with carbolic acid of increasing dilution. Other observers obtained satisfactory results by passing the bacilli through refractory animals.

**With other  
Acid-fast Bacilli.**

De Schweinitz attained a certain immunity in guinea-pigs by means of attenuated human tubercle bacilli; similarly Héricourt and Richet succeeded in man by means of avian bacilli. McFadyean [213] produced a high grade of immunity in cattle, both by injecting the products of metabolism of bacilli or their dead bodies and also by injecting living bacilli closely related to the tubercle bacillus, specially avian bacilli. Terre's experiments with piscine bacilli and Dieudonné's with frogs' bacilli both gave negative results. Encouraging results were given by Möller's [214] experiments with his acid-fast bacteria. Klemperer found in guinea-pigs a checking influence on the tubercular infection, but this was only temporary. Investigation in the Institute for Infectious Diseases with timothy, dung, pseudo-bovine and slow-worm tubercle bacilli confirmed this, but established only a delay in the appearance of the first symptoms of infection and in the course of the disease.

Klebs [215] concludes from his own experiments on animals that the infectious power of human tubercle bacilli is much attenuated by the antagonistic effect of slow-worm tubercle bacilli and has used this antagonism in the treatment of human



tuberculosis. According to Klebs the effect is due to the transformation of the infectious human tubercle bacilli into the form of slow-worm tubercle bacilli, which are not injurious to the warm-blooded body. The slow-worm tubercle bacilli are taken up by migratory cells and brought to the diseased organs. According to his latest communications [216] the internal method of application in the form of tabloids with lactose is quite satisfactory.

**Friedmann.** Friedmann [217] reports the immunizing action of his tortoise bacilli in guinea-pigs, but the period of observation was too brief, as the publication of Libbertz and Ruppel shows. Orth was able to confirm the fact that tortoise tubercle bacilli really belong to the group of tubercle bacilli and produce tuberculosis, though of a form with little tendency to progress; the guinea-pigs thus treated, however, only remained alive on the average longer, and some of them showed a relatively late occurrence of typical pulmonary tubercle with cavity formation. In a later communication Friedmann stated that he had succeeded in protecting two cattle by means of his culture against a subsequent infection with bovine bacilli.

**Friedmann's Method.** According to his latest publication, Friedmann [218] has succeeded in rendering a culture of tortoise bacilli (which already possessed but little power of causing morbid symptoms and was of low toxicity) so completely non-toxic that the living bacilli lost even the last traces of their power of producing symptoms and their toxicity, but still retained their specific curative substances. After he had proved its value by many animal experiments and their harmlessness for man by trial on his own person, the preparation has been used during the last few years in therapy for tubercular patients of all kinds in a large number of clinics.

**Results.** Up to the present 682 patients have been treated, including 250 cases of pulmonary tuberculosis, also glandular, skin, bone, joint, urogenital tuberculosis and scrofula. In almost all cases except those recognized as hopeless from the start the result was good when the preparation was properly absorbed. When it was not absorbed abscesses were even observed and the preparation was inactive. By alternate intravenous and subcutaneous injections these failures have lately been avoided. Pulmonary tuberculosis showed a regular and generally permanent improvement, both subjective and objective; long suppurating glands and fistulae were completely cured; tuberculosis of the joints gradually improved; cases of tuberculosis of the bladder and kidneys showed distinct improvement, and were sometimes completely healed; even lupus foci of ten years' standing showed progressive healing and scrofulous



exanthemata of long duration were permanently cured without other methods of treatment being applied. After these conspicuously successful results, which also proved the harmlessness of the method, 350 children from a tubercular district were given a single protective injection (intramuscular), with the result that all thrived splendidly, and since the injection a year ago have been free from all tubercular and scrofulous symptoms.

The therapeutic value of the preparation in surgical tuberculosis was confirmed in debate by E. Müller and Schleich, the former also stating its protective action in fifty-three sucklings. Karfunkel has treated 415 cases of various forms of tuberculosis in his Polyclinic for Tuberculosis. Since abscess-formation has been avoided the action has been favourable throughout; no harm has ever resulted; prophylactic injections have shown good results. Küster describes the results as surprising. P. Heymann also maintains its value; even in severe forms striking improvement was often observed. Blaschko found the remedy useless for tuberculosis of the skin with the exception of a very few cases. Bier, Goldscheider, F. Klemperer, Citron, and Konisch are reserved in their opinion. Wolff-Eisner has doubts concerning the protective inoculation. Schwenk could obtain no result in tuberculosis of the bladder and kidneys. Orth, in his experiments on animals, could not prove any healing action, but was only able to prolong the life of the animal.

The results obtained with Friedmann's non-virulent tortoise bacilli at all events call for continuance of the experiments, observing all the precautions necessary in the trial of a new remedy and with careful observation, preferably in a clinical institute. With regard to this protective inoculation, we feel bound to call for the most extreme caution on account of the doubts raised as to the nature of Klimmer's non-virulent tubercle bacilli, especially by Piorkowski, who is inclined to consider the so-called "Friedmann's tortoise tubercle bacilli," isolated in 1903, as weakened *human* tubercle bacilli.

**Calmette.** Immunization by oral administration of killed cultures, a method proposed by Löffler for typhoid protection, is recommended by Calmette [219]. On the basis of his researches into the absorption of tubercle bacilli from the intestine, in which he supported v. Behring's theory of the intestinal mode of origin, at the same time modifying it in essential particulars, he considers that he has rendered cattle and also man immune by two doses at forty-five days' interval of tubercle bacilli previously killed by moist or dry heat, or by chemicals. Laffert, on the other hand, was unsuccessful with guinea-pigs.

**Calmette and Guérin.** Calmette and Guérin have recently been able, by growth on ox-bile, to weaken the tubercle bacilli to such an extent that the subcutaneous infection of guinea-pigs only produced local



tuberculosis and that the intravenous injection of 100 mg. into cattle did not produce typical tubercles, but only a general feverish loss of condition. With these bile-weakened bacilli, the authors produced a high degree of immunity in cattle by means of an injection of 25 mg. once a month. It must be noted that the immune serum obtained from these animals did not display any protective or healing properties in guinea-pigs or cattle, though in the latter it prevented the development of tubercular foci to a certain extent.

**v. Behring.** v. Behring was able to produce in cattle a high grade of immunity to bovine bacilli by treating them with living human bacilli. The milk of such immunized cows he has recommended as a preventive against tuberculosis in infants. Koch and his co-workers are of opinion that "the possibility of protecting cattle is shown by v. Behring's experiments, but that they do not indicate any suitable method of immunization."

Ebeling, Lorenz, Roemer, Strelinger, and Schricker obtained successful results. Dammann, after careful experiments on animals, could only attribute slight protection to the v. Behring method. This was also the opinion formed by Hutyra and Eber. After the researches of A. Weber and Titze [220] of the Imperial Board of Health, all that can be said for the v. Behring immunizing process is that it increases the powers of resistance of the animal treated in favourable cases for about a year. But no practical value has been definitely proved to be possessed by this protective inoculation.

In a herd of cattle which had been rendered relatively free from tuberculosis by Bang's elimination process, tuberculosis spread after the treatment as quickly among the cattle protectively inoculated as amongst those not inoculated. A final verdict can only be based on the condition of large numbers of slaughtered cattle. The value of the tuberculin test repeated every year is doubtful, because the tuberculin reaction seems to become less reliable owing to the protective inoculation, and because the reactivity of the inoculated animals in diseased herds becomes weakened in consequence of the frequent opportunities of absorbing bovine bacilli.

**Vallée.** Vallée [221] achieved no better results with his method based on Behring's principle, in which he applied intravenously bacilli obtained from a horse. He obtained more effective protection by inoculating young cattle with small doses of virulent bovine tubercle bacilli or large doses of non-virulent bacilli by mouth (*cf.* Calmette). When animals so treated were brought into close contact with cattle suffering from open tuberculosis, they remained fully protected for a year; only



after two years did they show insignificant symptoms, whereas the control animals became very ill.

v. Baumgarten [222], by injecting human bacilli into calves, produced so high a grade of immunity that they were protected against a bovine infection lethal for control cattle. Recent research places the dose for practical purposes at 2 cg.

**Koch.** Koch and his co-workers [223] succeeded in producing complete immunity by means of injection of attenuated bovine cultures once repeated. They finally worked out a method by which cattle were rendered certainly immune against highly virulent bovine bacilli by means of a single intravenous injection of 1 to 3 cg. of human tubercle bacilli or of attenuated bovine. They are convinced that this method of immunization is intimately bound up with the specific difference of the bovine and human tubercle bacillus discovered by Koch.

**Tauruman.** Tauruman's preparation consists of living human tubercle bacilli in normal saline. A. Weber and Titze [220] tested cattle treated by Tauruman's method as to their power of resisting tuberculosis by intravenous and subcutaneous injection, by inhalation, by food and by natural infection (stall infection). No essential difference in the immunizing power of bovovaccine and Tauruman's preparation was seen at first. Later experiments appeared to prove the great superiority of the protective inoculation, but this was to be explained by the elimination of very important sources of infection (necessary slaughter of a cow suffering from tuberculosis of the udder, use of boiled milk) and not by the good effect of the Tauruman inoculation.

N.B.—It is very important to note that the intravenous injection of human tubercle bacilli may give rise not only to focal disease of the udder, but also to localized tuberculosis of the eye and fungoid disease of the joints. In three cases the bacilli of the *typus humanus* remained 2½ years in the cattle and increased without showing the slightest approach to the *typus bovinus*. The fact that human tubercle bacilli are retained in the bodies of cattle gave rise to precautionary measures with regard to the sale of meat of protectively inoculated cattle.

**Klemperer.** Klemperer [224] established by experiment on cattle that immunity may also be produced by subcutaneous injection of human tubercle bacilli. In a series of cattle artificially infected with bovine tubercle he saw a certain degree of favourable influence exerted by subsequent subcutaneous injection of human bacilli. Koch's teaching of the specific difference of the two kinds of bacilli induced Klemperer



to treat tuberculosis in man with living bovine bacilli, in an analogous way to the active immunization of cattle with living cultures of human bacilli. After he had convinced himself of the harmlessness of the infection by experiment on himself, as Carl Spengler had also done, he employed this method in cases of phthisis. Fifty-four injections were given to six patients. Local trouble was slight; four times an abscess formed, on several occasions a local thickening remained, in most the injection was absorbed without leaving anything behind. General disturbance was never observed; the patients even noticed subjective improvement and gained weight. These experiments, for which priority must be given to Carl Spengler, are certainly designed to turn the scale on the side of the correctness of Koch's teaching of specific difference.

**Roemer.**

Roemer's [225] experiments have thrown a good deal of light on the nature of human tuberculosis; by means of a weak tubercular infection, subcutaneous or intraperitoneal, he succeeded in protecting guinea-pigs, swine and sheep against a second infection with tubercle bacilli which was generally fatal for control animals. He also further proved [226] that this immunity to reinfection with tubercle bacilli held not only with respect to an artificial subcutaneous, cutaneous or intracutaneous reinfection, but also to methods of infection which either approach very closely the natural conditions (food and inhalation infection) or directly correspond to similar natural conditions (contact infection). He concludes from this, and his conclusions are based on clinical and statistical observations, that also adult human beings acquire from outside a considerable or perhaps even absolute protection against fresh infection with tuberculosis if, as children, they have recovered from a slight infection.

Webb, Gerald Bertram and Williams were even able to inoculate guinea-pigs with large quantities of tubercle bacilli without producing tuberculosis by making a first infection with an extremely small number of bacilli and gradually increasing it. After they had recently been successful with this method in the monkey (*Macacus rhesus*), which in captivity is extremely susceptible to tuberculosis, they have used it in small children of tubercular parents. The initial dose was 1 tubercle bacillus, the final dose 150. The children gained in weight and maintained an unbroken healthy condition; v. Pirquet's test was negative.

**Heymans.**

Heymans' method of protective inoculation consists in giving the experimental animals



little reed sacs containing dried human tubercle bacilli in gelatine capsules. There is no danger for men if the sacs are air-tight. According to present investigations, half the animals died. No opinion can as yet be formed as to the protective power of Heymans' method.

**Klimmer's  
Antiphymatol.**

Klimmer [227] has published a method of protective inoculation against tuberculosis based on the subcutaneous application of a non-infective material, Antiphymatol, a method attended with good results for some years at the Institute for the Study of Infectious Disease in the Royal Veterinary School in Dresden.

**Preparation.** To prepare the substance, human tubercle bacilli are completely deprived of their infecting power by long heating to  $52^{\circ}$  to  $53^{\circ}$  (weakened bacilli) or by passage through animals (avirulent bacilli). Since the spring of 1909, only the second method has been used. Antiphymatol does not regain its power of infection by remaining in the animal's body, is without danger in use and does not lessen the value of the meat and milk of the animals inoculated. Out of seventy-one inoculated animals, after a period ranging

up to four years, sixty-nine were found free from tuberculosis when slaughtered; in the two animals which showed slight tubercular changes, the previous tuberculin treatment had not been carried out in a very satisfactory manner. So that Klimmer's protective inoculation must be acknowledged as the best method known at present of protective inoculation and extirpation of tuberculosis (Johne).

**Curative Power.** Klimmer also succeeded by treatment with his non-infective substances in arresting and curing existing tubercular disease in cattle. Out of seventy-four cattle, introduced to stalls notoriously infected, twenty-five on inspection of the flesh after two to twelve months proved free from tuberculosis; in thirty-nine there was distinct encapsulation of the tubercular changes and a complete absence of new processes.

Subsequent tests by Weber and Titze on protective inoculation showed that in four cattle which had been treated the same tubercular changes had taken place as in the control animals. These authors state emphatically that if the improved theory of transformation by passing through cold-blooded animals be accepted, then the re-transformation from virulent to avirulent bacilli in mammals must be granted in theory; but they consider them to be saprophytic acid-fast bacteria, as are often found in cold-blooded animals.

In two different specimens Eber found the weakened human tubercle bacilli virulent for guinea-pigs. On this account Weber and Titze fear that



sufficient certainty as to their attenuation cannot be guaranteed in the manufactured preparation and consider there is danger in the annual repetition of the protective inoculation of fully-grown animals giving milk.

It must be noted that Klimmer rightly refuses to accept Eber's conclusions based only on experiments on two guinea-pigs; the resulting cessation of the use of the preparation made from attenuated human bacilli on purely technical grounds makes any discussion as to its possible danger superfluous. Doubts as to the harmlessness of antiphymatol have, however, been proved baseless according to the results of scientific research and practice.

**Authors'  
Experiences.**

Klimmer's success with cattle induced him to treat the human subject with good results. After we also had convinced ourselves of the avirulence of his preparation by subcutaneous, intraperitoneal and intravenous tests on rabbits and guinea-pigs, we made the same experiments as Klimmer to test the therapeutic value of his serum for tubercular men. From our experiments we can only deduce that the serum is borne without any reaction whatever; but we could not detect any effect whatever on the tubercular process. Klimmer is at work perfecting his method; he considers that hitherto much too small doses at too long intervals have been used. We shall renew our therapeutic experiments when opportunity occurs.

**Bartel.**

In connection with the therapeutic experiments of Klimmer with avirulent tubercle bacilli, the experimental work of Bartel [228] must be briefly mentioned, the results of which seemed to him important enough to serve as a point of departure of a successful process for specific immunization against tuberculosis. Bartel discovered that tubercle bacilli suspended in the organs—especially the lymphatic tissue—of healthy animals and kept for some time in the incubator, other micro-organisms being excluded, proved avirulent when inoculated in the organic tissue of guinea-pigs. After one or several inoculations, animals so treated exhibited considerable immunity to a virulent infection, even healing processes in organs already manifestly affected and absence of any tubercular changes in all parts of the body. According to recent researches of Bartel and his co-workers Neumann and Leimsner, ferments, oleic acid soaps and especially lipoids also act in the same way as the lymphocytic tissue (spleen, mesenteric lymphatic glands). Tubercle bacilli treated with these substances gave rise to processes of immunity in experiments on animals.

**Levy's Tebean.**

Levy used killed tubercle bacilli of the *typus humanus* in making his new remedy Tebean.



Virulent bacilli are shaken in 25 per cent. galactose for  $4\frac{1}{2}$  days at  $37^{\circ}$  C. and concentrated *in vacuo* until 1 grm. of powder contains 5 mg. of bacilli. The preparation, therefore, consists of whole bacilli killed or very much weakened by galactose. The solutions are prepared with normal saline always immediately before use. One begins with  $1/200$  mg., and gradually increases the dose at intervals of two to seven days, avoiding any severe reactions, reaching a maximum of 2-4 mg. At the site of inoculation small infiltrations are almost regularly formed which may last for weeks. The formation of abscesses has also been observed. Length of treatment about three months. Repetition of treatment should be made after a few months.

Levy and Krencker [229] and Steffen [230] have reported good results in severe cases, caseous-pneumonic and even acute, florid processes.

## (12) NASTIN AND TUBERCULO-NASTIN.

In connection with the remedies for producing active immunization it remains to mention the highly interesting researches of Deycke and Reschad Bey [231] on leprosy, which have had a certain influence on the course of tuberculosis research. Here, too, the researches of R. Koch on his TR are of fundamental importance.

### Streptothrix leproides.

It is well known that these authors obtained a pure culture of a streptothrix, *S. leproides*, from a severe case of leprosy. This organism is not identical with the leprosy bacillus, but with it they were able to attain extensive retrogression of the leprous process. Their researches led them to the conclusion that the organisms producing leprosy owed their parasitism principally to the fatty substances with which they were impregnated and that the retrogressive changes associated with the injection of living cultures in the leprous subject must stand in causal relation with this substance. It was therefore their aim to isolate from the cultures this fatty substance. After much laborious work they finally succeeded in producing a chemically pure fatty substance, which they called nastin, and which proved itself indubitably the active agent. The authors assume that the true lepra

### Nastin.

bacillus contains a fatty body identical with nastin or standing in close biological relation with it, that to this body the lepra bacillus principally owes its resistance to the antibodies in the organism and that nastin injections result in an active immunization against this substance. The question naturally arose as to whether in the case of other acid-fast bacteria, especially the tubercle bacillus, a fatty body similar to nastin could not be found. The attempt failed to obtain such a substance pure, and they then studied the working of their nastin in tubercular subjects. On the day following the injection distinct fever occurred, now and then of considerable height, the sputum often increased enormously and tubercle bacilli, even when previously scanty, appeared in great masses, with definite evidence of bacteriolysis. In spite of all this the therapeutic effect in general tuberculosis was less favourable. In healthy men and animals nastin is quite inert.



Later, Deycke succeeded in preparing from tubercle bacilli a neutral fat analogous to nastin, which he called tuberculo-nastin. From the successful treatment on the one hand of tuberculosis with nastin, and on the other of leprosy with tuberculo-nastin, Deycke deduced the chemical and biological identity of the two substances.

**Nastin-B.** In employing nastin in leprosy Deycke observed a certain inconstancy in the results, which he attributed to a lack of leucocytes. He, therefore, attempted to produce a leucocytosis, first by means of hetol and then with benzoyl-chloride, a form of benzoyl soluble in oil known in the trade as ketyn. In employing this combination of nastin with benzoyl-chloride, nastin-B, the results in leprosy became constant and in every way satisfactory, even in cases where nastin alone had failed.

**Clinical Results.** For the treatment of tuberculosis also these researches were of value. Deycke had noted that when pure nastin was employed too frequently in leprosy patients serious general disturbances, attended with fever, occurred as a result of the solution and absorption in bulk of the endotoxins and proteins contained in the lepra bacilli disturbances which could be set aside by ketyn. In tuberculosis also pure nastin was shown to be too dangerous on account of its bacteriolytic effect and Deycke employed instead benzoyl-nastin in a weaker dilution.

The results of the use of nastin-B have been considerably more promising even if they have not fulfilled all the expectations of Deycke himself.

**Recent Research of Deycke and Much.** From recent researches of Deycke and Much [232 and 233] it follows that nastin is a fatty body causing reactions, common to certain acid-fast bacteria and further that treatment with nastin alone is useless. On the other hand, they obtained no immunization from the albumin of the triturated tubercle bacilli applied alone, but did so after the addition of nastin. Therefore the authors considered the combination of fatty and albuminous bacillary substances in the treatment of tuberculosis as necessary and full of promise.

They succeeded with preparations of lecithin, made partly from cerebral substance and partly from egg, in producing complete bacteriolysis of the tubercle bacilli. With this preparation, which contained the dissolved bodies but no living bacilli and which they called Tb-L, they were able to protect guinea-pigs from tubercular infection by previous treatment. In the course of their researches they found great inconstancy in the different kinds of lecithin coming from the same factory, and it was proved that the bacteriolytic power does not reside in the lecithin, but in a substance as yet unknown bound up with lecithin. Only with difficulty (or not at all) have



they succeeded up to the present in the dissolution of bovine tubercle bacilli—a noteworthy fact in view of the unexplained opinions as to the specific differences between tubercle bacilli of warm-blooded animals.

**Bacteriolysis by Neurine and Choline.** Deycke and Much [234] later obtained complete bacteriolysis of the tubercle bacilli, accompanied by the dissolution of the albuminous matter and neutral fat, by means of choline and neurine.

Neurine is specially efficacious, 1 gram. of tubercle bacilli being completely dissolved by 10 gram. of neurine in two hours at 56° C., and very largely dissolved at 37° C. Jessen, Ditthorn, and Citron have confirmed this. According to Ditthorn, the washed bacilli which still remained undissolved in 25 per cent. of neurine after twenty-four hours no longer grow nor produce tuberculosis in guinea-pigs. Also, no specific substance can be shown to exist in the neurine solutions of tubercle bacilli by the method of fixation of complement.

**Latest Research of Deycke and Much.** In the further course of their researches Deycke and Much found that dissolution by means of neurine was too far-reaching, the specific immunizing substances of the tubercle bacilli being very considerably altered. According to their latest work, they have found almost all organic acids suitable which do not produce complete dissolution but only partial destruction of the tubercle bacilli, so that their albuminous and fatty substances are emulsified in the fluid and are still active as antigen. With these products, Much was able to produce hyper-susceptibility and also a high degree of immunity in a normal animal. Much and Leschke injected tubercle bacilli into the peritoneum of guinea-pigs previously treated with it and claim that direct bacteriolysis of the bacilli took place as in Pfeiffer's experiment. The Deycke-Much school is now testing the therapeutic value of this bacillary solution and is hopeful that it may finally prove a remedy of practical utility in soluble form. As, however, the therapeutic action of these preparations has proved very uncertain in man, Much's aim is directed to the production of immunity to all possible "partial antigens" in the tubercular individual. With Citron he assumes that the uncertain action of all tuberculin preparations, including those made by the action of organic acids on tubercle bacilli, is due to the fact that they do not represent a single uniform substance. According to his own researches and those of his students, the tubercular organism produces the particular antibodies for the bacillary protein and bacillary fatty bodies in a varying and very irregular manner.



The task of specific treatment must be to determine by the method of deviation of complement which "partial antibodies" are present in insufficient quantity and then to aid their formation by injection of the corresponding "partial antigens." In confirmation of these views, Borissjack, Sieber and Metalnikow [235] have shown by animal experiment that the most active antigens for the production of antibodies are tubercle bacillary wax, bacillary bodies freed from fat, and lecithin, alone or mixed; and they state, too, that these are not only antibodies for the antigens alone but also for living and dead tubercle bacilli.

### **(b) Preparations Designed to Produce Passive Immunity.**

#### **Serum of Refractory Animals.**

Besides the active method of producing immunity so far considered, the attempt has been made to cure tuberculosis by means of passive immunization, by allowing the diseased organism to assimilate ready-made protective bodies contained in the blood-serum of animals which had themselves been previously treated with tubercle bacilli or their products. The most obvious method consisted in the employment of the blood or serum of animals supposed to be immune. The blood-serum of animals artificially immunized by tuberculin injections was also tested on guinea-pigs. And a number of French authors report good results obtained in this way.

#### **Early Attempts with Serum-therapy.**

Other experiments in serum-therapy were undertaken by Trudeau and Baldwin with serum of immunized asses and sheep, as well as with serum from fowls and rabbits. The result of these experiments was negative, as also was the case with Auclair's on the serum of immunized fowls. De Schweinitz obtained an immunizing serum by treating horses, mules and asses with the products of tubercle bacilli. Horse serum was also used by Prioleau and Paquin, asses' serum by Redou and Chenot, Ferran, Dörrenberg, Babes and Broca. These and many other experiments in serum-therapy had but little result. It is worthy of note that Möller [214] could obtain no result with Ferran's serum in man, and that in the case of guinea-pigs treated with a potent goat-serum of his own a subsequent infection with tubercle bacilli produced a more rapid and fatal termination than in the controls. Mention must be made of the



experiments of v. Behring on a tubercular antitoxin prepared by himself. By gradually increasing doses he succeeded in immunizing tubercular cattle against doses of tubercular toxin fatal to healthy cattle. The serum of these animals contains only minute quantities of antitoxin.

Koch also, who in general stands for active immunization, tested the curative action on man of sera possessing high agglutinating power, but with no satisfactory result.

We shall not describe a number of recent attempts to produce an active antitubercular serum (Zeuner, Lannelongue, Bruschetini, &c.), which have occasionally given satisfactory results but are still in the experimental stage. We shall only discuss the more known sera and the results obtained with them.

### (13) MARAGLIANO'S SERUM.

#### Based on his Theory of Immunity.

In its preparation Maragliano [236] was led by the following considerations in regard to the pathogenesis and pathology of tuberculosis.

All the changes produced in the body by tubercular infection proceed from the toxins secreted in the body by the living tubercle bacilli and contained in their bodies. These toxins or proteins favour the spread of tubercle bacilli in the body. The body's natural means of protection, which are contained in the tissues and body fluids as well as in the blood serum, possess antitoxic, antibacterial and agglutinating powers. These three protective properties of the serum can be progressively raised when tubercular substances are assimilated by a healthy animal. The serum containing these bodies is suited for immunization and for curative treatment and stimulates the production of further protective bodies. After endless experiment he found the best method of producing a serum rich in antibodies to be the injection of a filtrate of young and virulent tubercle cultures, combined with a watery extract of virulent dead bacilli. For the treatment of the animals designed to provide the serum he used, then, both the bacillary toxins and their actual bodies.

#### Animal Experiment.

Horses, cows and calves proved the most suitable animals and the injections were continued for six months. The serum of these animals protects guinea-pigs and rabbits against an otherwise lethal infection with living tubercle bacilli. In his researches there was an increase in the antibodies in the serum of the animals and tubercular patients treated, the symptoms of toxæmia disappeared, nutrition improved and the objective symptoms of the tubercular process were relieved. He estimates that some 20,000 tubercular subjects have been treated with his serum. Mircoli gives the

**Clinical Results.** following statistics of 2,899 cases so treated: of 250 cases of limited afebrile disease, 38 per cent. were cured, 49 per cent. improved; of 938 cases of limited febrile disease, 18



per cent. were cured, 54 per cent. improved; of 665 cases with diffuse tubercular broncho-pneumonia without mixed infection, 14 per cent. were cured, 43 per cent. improved; of 332 cases with diffuse broncho-pneumonia with mixed infection, 9 per cent. were cured, 36 per cent. improved; of 712 cases with cavity formation, 6 per cent. were cured, 40 per cent. improved; an average of 17 per cent. cures and 44.4 per cent. improvements. Of these patients 2,396 were febrile; fever disappeared in 1,111 cases, or 46 per cent. In some cases the cure had lasted seven to nine years.

Maragliano wishes to restrict the application of his serum to the early stages of tuberculosis. To the general question of the fight against tuberculosis he takes up the position of prophylactic therapy. His results from active immunization, from which he expected no success, may be passed over as well as a method of vaccination akin to Jenner's which he elaborated.

**Conflicting  
Evidence.**

Success with Maragliano's serum is confirmed by Crotto, Hager, Carlucci, Dasara, Ulrich, de Renzi, Cattaneo, Fasano and others. Mafucci and di Vestea saw no result; and Möller and Krause nothing appreciable. The result of two years' experience with the serum in the Henry Phipps' Institute in Philadelphia seems also to have been unfavourable, also the results of Flick and Lardis given at the International Congress on Tuberculosis at Washington. Recently, however, the Maragliano school again reports successful results. Marzagalli and Figari cured an ape with advanced disease and confirmed the occurrence of scarring and calcification by autopsy. Cambiaso cured a severe case of pulmonary tuberculosis by 116 injections, which he was able to confirm one and a half years later.

Of his pupils, Livierato proved by experimental tuberculosis in animals that the progress of the infection was hindered. Added to bacilli *in vitro* it weakened their virulence and power of development. The blood-serum of tubercular patients showed no inhibiting influence on experimental tuberculosis in animals, but favoured its development.

Adherents of the Maragliano school—Mircoli, Sciallero, Marzagalli—have demonstrated degenerative changes in the tubercle bacilli as a result of the action of antitubercular serum, and these are of favourable prognosis for the individual treated. Goggia confirmed this in one case clinically. Ghedini recommends, in cases of tubercular disease of the joints and testes, the direct local injection of the serum.

Favourable results have further been recorded by Giordano, Rapallo, de Paoli, de Barbieri, Angelo, Piola, Chmelar and Mitulescu.



## (14) MARMOREK'S ANTI-TUBERCULAR SERUM.

**Relation of  
Tuberculin to True  
Tubercle Toxin.**

The nature of the tuberculin reaction being not yet fully explained, and its action varying so widely in the different stages of the disease, Marmorek [237] was led to take up the view that tuberculin is not actually the toxin of the tubercle bacillus, but that it stimulates the recipient to produce another toxin in greater quantity.

**Special Culture  
Medium for  
Primitive Bacilli.**

On his theory there are two different stages of the tubercle bacillus and different secretory products depending on the nature of the culture medium. The production of the true tubercle bacillus toxin is greatest from what he calls "primitive bacilli." He grows these on a medium containing "leucotoxic" serum and extract of liver tissue. In preparing this complicated medium he went on the assumption that the presence of leucocytes stimulates the production of tubercle toxin, and that animal experiment has shown that increase of tubercle bacilli and formation of tubercles occur only with difficulty in liver tissue. The presence of liver extract in the culture medium results in the bacilli retaining their "primitive" character for a longer time. The bacilli cultivated in the primitive stage increase rapidly on the medium. In these primitive cultures, the "primitive" toxin, the real tubercle bacillus toxin, differing in nature from Koch's tuberculin, is formed in great quantity. Koch's tuberculin, in the process of immunizing animals, produces only anti-tuberculin and remains inert towards other toxins of the tubercle bacillus; these latter are influenced by the toxin of the primitive bacilli. With some 30 c.c. of this toxin he was able to immunize guinea-pigs against an otherwise lethal dose of virulent bacilli.

**Clinical Results.**

Marmorek then employed his serum on man and treated severe cases of tuberculosis, especially surgical forms, with success. He recorded the cure of several cases of Pott's disease with fistulæ and abscesses and others with perforation of the intestine.

**Conflicting  
Evidence.**

In other hands the remedy has been very variously judged. Dieulafoy gave an unfavourable opinion, obtaining no immunity in animals and in man rather harm than good, as also Championnière. Hallopeau, in cases of cutaneous tuberculosis, observed the development of new nodules and wearisome suppuration at the sites of injection.

Definitely bad results are recorded by Krokiewicz and Engländer; by Stadelmann in five cases, and by Mann in twenty-three cases of pulmonary tuberculosis; by Meyer in three cases of laryngeal disease. Hodesmann, de la Camp, Deneke regard the remedy with suspicion. No success was obtained in pulmonary tuberculosis by Mackenzie, Rubinstein, Ganghofner,



Preleitner, Meissen, Szurek, Jereslaw, Wolman and M. Elsässer. The last named recently [238] showed the incomparably greater curative effect of the bacillary emulsion over Marmorek's serum, the latter having almost completely failed in twenty-five cases.

Unequal results are recorded by Jacquerod, Veillard, Stephani. Others, as Sievers, Holmström, Mannheim, Holmboe, Grüner, Strauss, Damanski and Gittelmacher, Ritter, Kroner, Sokolowski and Dembinski, John Mitchell express themselves with great reserve. Its value in pulmonary tuberculosis is attested by Lewin, v. Rothschild and Brunier, Lemieux and Richer, Veillard, Dubard, Latham, Jacquerod, Klein and Jacobsohn, Steinsberg, Müller, Morin, Petit, Feldt, Ullmann, Schenker, Wohlberg, Röver, Uhry, Horner, Vos, Germani, Cambiase, Castaigne and Gourand, Postnikow, Masenti, Roque, Nové-Josseraud, Robin, Klose. The best results were obtained by Montalti and even in advanced cases by La Neelle and Cornières, Faraggi, Kokler, Lévy and Jacobsohn. Pfeiffer and Trunk record entirely satisfactory results in twenty-four cases of open tuberculosis, some of them with laryngeal complications. Roblot saw good effects in all afebrile cases, all his failures being febrile. On the other hand, Mongour finds it valuable just in acute febrile cases of the 1st and 2nd but not the 3rd stadium.

**Elsässer.** F. A. Elsässer, too [239], records with enthusiasm unusual success in febrile cases of pulmonary tuberculosis, acute and subacute. Most favourable of all are the reports of surgeons in cases of surgical tuberculosis (*cf.* pp. 265-269).

**Frey.** Much better results with the serum seem to have been reached since it has been given *per rectum* on Frey's suggestion [240]; he has reported excellent results on the basis of 5,000 rectal injections. He observed undoubted specific influence on the local tubercular process, striking reduction of fever and improvement of the general condition.

**Schenker.** Schenker's observations extend to sixty cases of pulmonary tuberculosis mostly of the 2nd and 3rd stadium, tuberculosis of the bones, kidney and bladder in which he used the serum, which he considers less irritant and more lasting, with good results. He considers the subcutaneous method more certain and only recommends application *per rectum* when for some reason or other the subcutaneous method cannot be borne.

**Köhler.** Köhler [241] reports very unequal results in spite of rectal application in sixty more



advanced cases. In twenty-two cases an improvement, sometimes only a slight one, was noticeable in the condition of the lung, in thirty-eight cases it remained unfavourable or was distinctly worse; scarcely in a single case did the serum treatment lead to the removal of the tubercle bacilli from the sputum. Examination after two years gave a completely negative result in forty-four cases, of which death occurred in thirty-three.

**Thorspecken.** The good results of Thorspecken after prolonged out-patient treatment were only observed in Stadium I and in closed tuberculosis of Stadium II, that is in cases of less severity; for the most part the serum was without effect.

**Kaufmann.** Kaufmann [242] considers the antitoxic substance in the Marmorek serum to be inert on the tubercular lung process. He attributes the disagreeable and harmful symptoms occurring in half of his cases to the foreign albumin of the horse serum. The disturbances generally took the form of heart trouble with high pulse, sometimes considerable fever and interference with the general well-being, also stomachic and intestinal trouble. He also thinks some cases of nephritis may be attributed to the assimilation of the foreign serum. He was unable to detect any influence on the organism by means of Arneth's blood pictures.

**Turban.** Turban [243] considers the serum to be a specific remedy, beneficial in a limited number of fresh cases of tuberculosis of the lungs and other organs, but does not immunize; in slight subfebrile cases it sometimes reduces the fever; in advanced cases it is of no use, and may, in his opinion, produce acute exacerbation.

**Monod.** Monod [244] deduces from his collection of the literature on the subject that the serum is both harmless and effective in all kinds of tuberculosis, and that if applied early it often produces a complete cure in surgical tuberculosis and marked improvement in pulmonary tuberculosis. At the session of the Académie de Médecine in January, 1909, he reported on ninety-three publications with a total of 1,379 cases of internal and surgical tuberculosis; 65 per cent. of the internal cases were favourably influenced, 72 per cent. of the surgical.

**Marmorek.** According to Marmorek's last publication [245], up to the present 10,000 cases have been treated (1,700 are described in 120 publications). The serum has been improved by the addition of an antistreptococcal component and a substance bactericidal for tubercle bacilli.



"Hypersusceptibility is avoided by application *per rectum*. There are no contra-indications for the use of the serum. It is of great therapeutic value even in advanced cases; even ten cases of tubercular meningitis have been cured by it."

**Injection into Diseased Focus.** Lately A. Schnöller has recommended the injection of Marmorek serum into the diseased focus; he reports the cure of two tubercular abscesses and a good effect on two cases of lupus and scrofuloderma. He also considers the intrapulmonary injection of serum in phthisis as full of promise on the ground of his own experiments. Jacobson cured two cases of tuberculosis of the bladder on the same principle by instillation of the serum in the bladder and attained encouraging results by direct injection into tubercular glands, a tumor albus and a cold costal abscess.

**Conclusion.** In reviewing the experience at present obtained with Marmorek's serum, one is drawn to the conclusion that a final verdict with regard to its curative value cannot yet be given. In many cases of fresh and purely local tuberculosis it is of value; outside this, its activity seems to be limited, especially owing to the mixed infection so often present in tuberculosis.

According to recent experiments by Hamburger and Monti, Escherich, Sternberg, Breton and Petit, Breton and Massol, on the production of antibodies by rectal assimilation of antigens and on the absorption of antibodies injected *per rectum* (tetanus toxin, tetanus antitoxin, diphtheria toxin, diphtheria serum, cobra antitoxin), it appears doubtful whether the antitoxins of Marmorek's serum are absorbed when thus administered.

### (15) HOECHST TUBERCULAR SERUM.

**Preparation.** In spite of the somewhat discouraging results of antitoxic serum, the Hoechst Farbwerke have themselves undertaken the preparation of a new serum for tuberculosis on new principles, of which full details have recently been given by Ruppel and Rickmann [20]. They worked on the assumption that the methods used to obtain antitoxic tubercular sera till then had been based on a false conception of the nature of tuberculin. As tuberculin develops its toxicity only in an organism affected by tuberculosis only individuals susceptible to tuberculin should be used for the production of anti-tuberculin. Animals suffering from tuberculosis were not suitable for the experiments because of their low power of resistance and also because of the difficulty of diagnosing the extent of the



disease and of limiting its course. Therefore for the preparation of effective tubercular sera, cattle, horses and mules, susceptible to tuberculin, were treated with tubercle bacilli or their derivatives. The susceptibility was produced by intravenous injections of living, foreign tubercle bacilli. In the blood serum of the immunized animals all known antitoxins appeared—agglutinins, precipitins, opsonins, bacteriotropins and the specific amboceptor antituberculin.

**Summary of  
Properties.**

Ruppel and Rickmann summarize the characteristics and action of the tubercular serum as follows:—

It completely deprives tuberculin and ground tubercle bacilli of their toxicity for tubercular animals.

By its effect on ground tubercle bacilli, non-toxic products arise which effect fixation of complement without the assistance of specific amboceptors. These tubercle bacilli, saturated with immune bodies, are described as sensitized.

Five cubic centimetres of the tubercular serum have prevented the origin of tuberculosis in a number of healthy guinea-pigs infected with virulent tubercle bacilli.

The serum appears to have a beneficial effect upon tubercular guinea-pigs.

It is well borne by tubercular men. Experiments to prove its therapeutic power have been successful in spite of the difficulties met with in the treatment of a chronic disease with serum.

In order that the immune bodies of the serum may be used without danger in the treatment of human tuberculosis, the sensitized tubercle bacilli should be employed in the form of an emulsion (*cf.* sensitized bacillary emulsion, pp. 173 to 175).

**Sobotta's  
Experience.**

The only reports of its therapeutic action at present available are those of Sobotta [246]; in a somewhat small number of patients treated with it he observed an improvement of the general condition, frequent facilitation of expectoration and especially a considerable and often even astonishing improvement of appetite; he did not, however, observe any influence on pulmonary hæmorrhage or night sweats, nor any perceptible improvement of febrile symptoms.

According to various unpublished statements, the serum has been employed in varied cases of tuberculosis, both slight and severe. Subcutaneous injections of 25 c.c. are the rule, repeated every four to six days. If for any reason longer pauses must be made between the injections, care must be taken to avoid anaphylactic symptoms. This can best be done by giving, in



these cases, a small dose of 0.01 to 0.05 c.c. on the same day as and previous to the regular dose. No statements of serious anaphylactic conditions have been recorded; a few cases of serum exanthema have been observed. Reports are in general favourable; a small number of authors have observed febrile symptoms after the injections.

### (16) STREPTOCOCCUS SERA.

#### Rôle of the Secondary Infection.

The fact attested on all sides that the course of chronic tuberculosis of the lung is aggravated by secondary infection due to organisms other than the tubercle bacillus and that this secondary infection makes the prognosis worse and the application of specific treatment more difficult or even inert, has led to the preparation of sera to act against these chronic mixed infections. They were originally directed not against the mixed infections of pulmonary tuberculosis, but against other local and general infections: staphylococcus serum against staphylococcus infections, especially lymphangitis; pneumococcus serum against pneumonia and ulcer serpens of the cornea; streptococcus serum against erysipelas, puerperal fever, angina, phlegmons, pyæmia, scarlatina and acute rheumatism.

#### Marmorek's Monovalent Serum.

Marmorek [247], who made the first comprehensive attempt to prepare a streptococcus serum, put forward the view that all varieties of streptococcus in human infections due to this organism are of one and the same species and that a serum must influence in the same degree all varieties. He raised the virulence of an angina streptococcus by passage through animals, and with this culture treated horses and sheep; with the serum of the latter many French clinicians, particularly Marmorek and Bordet, obtained good therapeutic results. Subsequent tests made in Germany (*e.g.*, by Petruschky, Aronson, and F. Meyer) showed the serum quite valueless. To-day it has only an historical interest.

#### Polyvalent Serum.

The reasons for the non-activity of the *monovalent* Marmorek serum were shown by Denys and van der Velde to depend chiefly upon the variation in species of human streptococci. They therefore used the most widely different strains of virulent streptococci and thus prepared the first *polyvalent* serum. Tavel then showed that the raised virulence of the cultures due to multiple passage through animals is a drawback, since this causes the



formation of antibodies differing considerably from those really required. In the preparation of his polyvalent serum, he therefore omitted the passage through animals and used streptococcus cultures as fresh as possible.

**Aronson's Serum.** Aronson [248] originally took up Marmorek's standpoint that the streptococci of man and animals are identical. By long treatment of horses with cultures of streptococci, the virulence of which had been raised by passage through animals, he obtained a serum of marked activity in animal experiment. Later he used varying strains pathological both for animals and man.

In individual cases good results have been seen from this serum in streptococcus mixed infection in phthisis; it must be used soon after the commencement of infection, a moment difficult enough to determine.

**Menzer's Serum.** Menzer's streptococcus serum [249] is prepared by treatment of horses with streptococci cultivated from the tonsils of patients suffering from acute rheumatism. Menzer adopted the standpoint that a serum active for man must be prepared from streptococci pathogenic to man and intentionally avoids passage through animals. With this serum he has obtained good results in chronic streptococcal mixed infection in cases of pulmonary tuberculosis and Ostrovsky has repeated and confirmed these results.

**Hoechst Serum.** The streptococcus serum made by the Hoechst Farbwerke is prepared by the immunization of horses with virulent streptococcus cultures. Only human cultures from the most varied streptococcal diseases are employed which are pathogenic for animals. By special culture methods the pathogenicity for animals is maintained always constant and this without passage through animals, since this produces marked changes in human streptococcus cultures. Thus with *a priori* virulent original strains a multivalent streptococcus serum is prepared. In order to make the immunization as effective as possible, the horses are first given a sufficient "ground immunity" by treatment with a highly virulent strain passed through animals. Then each horse is immunized with the original virulent cultures. After immunity has been attained, the sera of all the horses are mixed.

Zangemeister [250] attributes the poor effects of the present anti-streptococcus sera to the differences in complement or artificially produced amboceptor or both in man and animals. He hopes to obtain better results with an immune serum prepared from the ape, which he is now engaged in making.



### (c) Vaccine Treatment.

Vaccine treatment, inaugurated by Wright, at first received with enthusiasm in England and America, has not received much attention in Germany until lately. This was due, on the one hand, to the very difficult technique involved in the continuous control of the opsonic index, on the other hand to the doubt, not without justification, whether the value of the procedure justified the time and trouble expended. Lately vaccine treatment has been made simpler by the employment of a polyvalent stock vaccine prepared in the factory.

Study has been made of vaccine treatment in tuberculosis, especially of pulmonary tuberculosis accompanied by various forms of mixed infection, as to the nature and importance of which opinions are still divided. So attempts have been made to render the body immune to the various bacteria which accompany tuberculosis by injection of corresponding vaccines. We will just mention a polyvalent streptococcus vaccine which is on the market and Wolff-Eisner's mixed vaccine made from polyvalent streptococci, staphylococci and pneumococci. No authoritative statements of their efficacy have yet been published.

### (d) Carl Spengler's Treatment with Immune Blood (IK).

#### Immune Bodies formed in Bone-marrow.

In the present condition of inquiry into the question of immunity, it is believed that in natural and artificial immunization the specific protective substances are formed in the blood-making organs, chiefly in the bone-marrow. Observations have been made according to which extracts from the organs of immunized animals have proved experimentally more active than the serum. According to Pfeiffer and Marx, the spleen, for instance, of animals immune from cholera is four times more efficacious than the serum and the protective substances appear in it when there is no trace of them whatever in the serum. Schroeder [251] and his co-workers [252] have treated tubercular guinea-pigs with the pulped spleen of vaccinated rabbits and calves and discovered that the spleen contains protective substances against the tubercle bacilli, which adhere to the cells. The whole field of organotherapy shows how much was expected from this method, not for infectious diseases alone, but for all branches of medicine. It is possible that the reason no effective



process of immunization has yet been arrived at by this method is that disintegration by crushing, extracting and pressing is incomplete. Perhaps the fermentation method lately inaugurated by Heim has more hopeful prospects and may lead to a perfecting of sero-therapy by cytotherapy. But even to-day there is no certainty as to which cells really form the protective substances in the organs; in general, it is assumed that leucocytes transport bacterial products to the blood-making organs, where the immune bodies are formed.

#### Principles of IK Treatment.

Now Carl Spengler [253] thinks to have proved that the red blood cells are the site of the production and collection of the protective substances in a number of infectious diseases (*e.g.*, leprosy, suppurations, cerebrospinal meningitis, syphilis), but especially in tuberculosis.

The real producers of immunizing substances are, according to Spengler, the red blood corpuscles, which, stimulated by antigen with active hæmolysis, pass on their immunizing substances to the serum, which alone carries immune bodies for consumption. The white blood corpuscles and the blood platelets are centres of accumulation of the second order.

The tubercle immune blood of artificially immunized men and animals proved to its discoverer a splendid therapeutic remedy for tuberculosis. He calls the preparation IK. It contains the immunizing substances chemically pure, free from albumin and blood-pigments.

It must be specially noted here that up to the present it has not been possible to produce antitoxins and specific immune bodies in general free from albumin.

#### Nature of IK.

IK is acid, animal immune blood. It is obtained from rabbits which have been immunized against the most varied human tubercle bacilli, chiefly *Bacillus humano-longus*. The blood is obtained by puncture of a vein and received into carbolized saline solution containing lactic acid [254].

#### Properties of IK.

According to Carl Spengler, IK has a direct antitoxic and therefore direct antipyretic and a lytic bactericidal property. The lytic power may apparently run counter to the antitoxic and cover it, as it may give rise to reactive fever, when masses of virulent bacilli set free absorb the toxins, but are not fully combined. The lytic action is also seen indirectly in the removal of fever by decreasing the vitality of the bacteria.

Treatment with immune bodies is not a purely passive method of healing, but a passive-active one, as the lysocidins dissolve the germs of infection, so that on absorption their toxins are employed for the active increase of immunity.



### Spengler's Reports.

Carl Spengler reports results never yet obtained with other methods: the removal of fever is accomplished even in cases apparently hopeless, and this in a surprisingly short time. He states that one of the most striking effects is the rapid diminution of the tubercle bacilli, which were often only occasionally found after eight to fourteen days of treatment, even when present in large numbers at first. Even the most severe cases of phthisis can be treated when other methods offer no prospect of salvation, and many a case of the worst type can be cured.

### Conflicting Reports from other Observers.

Gernsheim, Dresdner, Rudloff, Bergeron, Brauns, Mitulescu, Pumr, Lukin, Simon, Peters, Benöhr, Hoffmann and Willers report favourably on IK in cases of pulmonary tuberculosis. Moritz Wolff recommends it for outpatient treatment of initial cases in children. Selter observed great subjective and objective improvement in children with tuberculosis of the glands and joints, also Westphal in febrile, acute phthisis, in two cases of tuberculosis of the knee-joint and one case of peritoneal tuberculosis. Casteigno states that he has observed complete cure of double tuberculosis of the kidneys under IK. Apart from the somewhat fantastic records of Carl Spengler's co-workers, the remaining favourable reports of IK are chiefly from abroad and therefore uncontrollable (Aravandinos, Autokratoff, Kiralyfi, Manujloff, Hollos, Castaigne and Gouraud, Wollston, Ryan, Matson, Griffiths, Wein, Wallerstein, Kirschenblatt, and the uncritical report of Herzberg [255]).

A section of the adherents of IK seem to be receding from the early enthusiasm which welcomed its appearance. It is now admitted that it has only exhibited a really striking effect in a small percentage of cases treated with it; it is now regarded as efficacious in tubercular intoxications, improving the general condition, allaying night-sweats and reducing subfebrile temperatures and regulating the stools.

Weintraud, Schaefer, Roth, Kerlé, Gantz, Weihrauch, W. Neumann, Benker, Karpilowsky, Szaboky, Scharl, Starkloff, Breuer, Koch, Meissen, Pigger, Galecki and Budrynski have not recognized any favourable results in adult pulmonary tuberculosis, some no specific action whatsoever. Baer, on the ground of his investigations, gives a decidedly unfavourable judgment of the remedy; he observed objective deterioration in the condition of the lungs and larynx, decrease in weight, albuminuria and signs of intoxication. Alexander and Kraft, too, have observed changes for the worse in the condition of the patient.



Exner and Lenk state that it has no effect in surgical tuberculosis. Pick has not been able to obtain the slightest action in cases of ocular tuberculosis.

#### Authors' Results with IK.

We ourselves have used IK on about 270 patients and especially in cases of open tuberculosis in Stages II and III, to a considerable extent complicated with slighter or more severe tubercular localizations in other organs, considering these the most suitable test cases.

We went more thoroughly into the testing of IK on a large scale after we had obtained more detailed information as to the theory and its practical application in Davos on the invitation of C. Spengler. This guaranteed the most absolute uniformity in our method of work. The need for a more efficacious remedy, especially in the advanced febrile forms of tuberculosis, was evident, all the more as IK was applicable even in the most severe forms of phthisis, and it was a question of inoculating ready-made immune bodies which required no work from the organism in preparing specific protective substances. We have given a detailed account of our laborious researches over a period of fifteen months [256 and 257]. The summary of our results is as follows:—

#### Summary.

No definite antitoxic effect was ever noted, either where there was slight or high fever; nor could immunization or even a weakening of toxic susceptibility to tuberculin be proved. As regards the lytic effect of IK we failed to note any constant, regular effect on the temperature, quantity, bacillary content and virulence of the sputum. We could not determine a distinct curative influence of IK in cases of tuberculosis of the lungs, larynx, skin, intestine, glands, bones and joints, nor a focal reaction in any localizations of the disease. We worked successively with eight different blood solutions, which represented progressive improvements in the preparation of which some were intended to have a more antitoxic effect, some a stronger lytic effect. All these preparations were equally negative in their effect. From our experience, based on the most careful clinical observation of about 270 cases treated according to C. Spengler's directions, *we must report that IK is absolutely inert and valueless for the treatment of human tuberculosis.*

#### IK Harmless, but Inert.

As regards the harmful effects of IK, reported from some quarters, we must again assert that we also have observed during the treatment many disturbances of general well-being, periods of fever, hæmorrhage and deterioration in the condition of the



lungs, but we did not consider it in any case justifiable to look upon the IK injections as the cause of these phenomena. The above-named phenomena are everyday complications in the natural course of advanced cases of tuberculosis. Among the large number of cases with which we have to deal, such phenomena must necessarily occur with a certain regularity and conformity to law. But although we actually tried to provoke a specific reaction in slight and in most severe cases with the smallest and with enormous doses, at times when the patient was at his best with undoubted power to react, and in critical periods, yet IK remained in every respect absolutely inert.



## B.—Special Section.

### A Specific Remedy Independent of Localization.

THE general change of view with regard to the value of the specific treatment of tuberculosis dates from barely ten years ago and was chiefly brought about by lung specialists. Hence the telling results are chiefly in the province of pulmonary tuberculosis. By slow degrees specific treatment was tried for other tubercular organs and many successful results are recorded. For practical purposes it is necessary to chronicle these results separately under the respective organs, so as to get a clear idea of the significance of specific treatment in tuberculosis of the various organs. It is obvious that whatever the localization of a disease process, if the same infecting agent is at the basis of it, a specific remedy must in the nature of things have the same curative value, assuming that the anatomical changes concerned as well as the function of the organ involved and the acuteness of the process allow of the possibility of a cure. Now we shall see that the results with the various organs is not everywhere uniformly favourable. Apart from the actual possibility of cure in itself, the localization of the process plays by no means a secondary part. But above all—and this point seems to us far too little emphasized in describing the possibilities of the specific treatment of other organs—it is a question of the amount of disease in the lungs. Primary tuberculosis of an organ with healthy lungs is seldom seen, the disease generally proceeding from the lungs or their glands; in many cases the pulmonary disease is not only the basis but also the chief localization and determines the prognosis. From this it not only follows that specific treatment of all organs must be carried out with constant consideration of the pulmonary disease, but also that the display of its activity on the secondary tuberculosis of an organ is limited in proportion to the prominence of the pulmonary disease and the extent and freshness of the disease in the tissues. The larger mass of tubercular pulmonary tissue absorbs the remedy injected by reason of its avidity in proportion to the susceptibility of its cells to the toxin, and only allows it to act on the secondary



focus in a lesser degree and late. To know and recognize this fact is necessary both for correct specific treatment and for competent criticism.

A second point is also important: Whatever one's attitude to the question of mode of infection and primary disease of the organism, the lung is the favourite organ for the ravages of tuberculosis with which *alone* the organism may be able to cope, even when the disease is relatively extensive. If a secondary focus develops in another part of the body, this is the expression of a weakening of the power of resistance of the organism, and it makes the general prognosis of the doubly threatened individual worse. This fact must also be remembered in questions of the specific treatment of secondary tuberculosis of other organs and in judging of its value.

#### Possibility of Harm.

Now the question has arisen whether there is not some danger possible to one or another of the various organs in specific treatment. In the Theoretical Part we have given a detailed account of the anatomical healing processes, and shall again return to the question in describing the specific treatment of the several organs. Here we may say that in general the possibility of destruction of tissue occurring must be taken into account. But since the aim of the modern application of specific remedies, as has been already set out, is only to invigorate and assist the natural healing processes, the danger involved will not be other than that conditioned by the natural course of the disease in the particular organ.

As we have seen, specific treatment can be carried out with remedies both for active and passive immunization. The latter stand, both in efficacy and importance, a very long way behind the tuberculins intended for active immunization. Therefore in describing the specific treatment of the several organs, tuberculin treatment will always take the chief place. Where serum treatment has proved successful, this will be mentioned at the conclusion of the separate chapters in cases where this has not already been done under the section on Passive Immunization.

### 1.—PULMONARY TUBERCULOSIS.

All the experiences which we have collected in the Theoretical Part with regard to the principles and technique of tuberculin treatment have chiefly been concerned with our studies in the treatment of pulmonary tuberculosis. There remains nothing further to be said on this head. A detailed description necessi-



tates, however, a consideration of what cases of pulmonary tuberculosis are suitable for tuberculin treatment.

**Indications:**

**Earliest Possible**

**Application.**

Koch lays the greatest stress on the earliest possible application of the remedy. The early stage of phthisis is the proper object of treatment, because at this stage tuberculin exerts its full and complete action and, as he assumes, can effect a certain cure. This warning of Koch's, which was entirely forgotten in the first tuberculin era, was strongly emphasized by all those who were instrumental in reintroducing the method. In the opinion of certain opponents of the method the limits were so closely drawn that only the most favourable cases were so treated and this selection entirely explained the alleged superiority of tuberculin treatment. These are, of course, idle contentions long since set aside. If the oldest and most experienced adherents of the method insisted over and over again on a more strict selection of cases, it was only to warn against the old mistakes and avoid a repetition of the same mishaps in the new therapy. According to the present-day view, uncomplicated

**Selection of**

**Cases.**

afebrile cases of pulmonary tuberculosis in Stadiums I and II of Turban are suitable for tuberculin treatment. The limitation is evidently based on the practice of the popular sanatoria in regard to admission of cases and includes the material in which working ability is likely to be regained in the usual duration of treatment (three months). If this period be strictly adhered to, then in point of fact the sphere of action of tuberculin will have been nearly exhausted. But it hardly seems correct to measure the therapeutic value of a remedy by means of a variable time-period, applicable only to a section of the population and dependent on the momentary position of social polity. The sphere of tuberculin is, in fact, a much wider one, with, of course, certain natural limits. Tuberculin is no panacea for all forms of tubercular disease. It is not even directly a curative agent at all in the sense that antidiphtheritic

**Tuberculin an  
Active Immunizing  
Agent.**

serum is; it is an active immunizing agent. In the first case the organism receives something ready-made and requires to make no effort of its own; in the latter it must engender a reaction due to the introduction of the products of tubercle bacilli, and this reaction leads to the appearance of protective bodies. In tuberculin treatment, then, the body has first to produce antibodies; it must prepare its own specific protective substances. Labour is involved, which presupposes a certain store of strength. Hence, in the first place, all individuals



are to be excluded whose vigour is much reduced, an exclusion pretty much conterminous with the forms of severe mixed infection. Tuberculin can exert no curative action on the secondary purulent processes caused by the streptococcus, pneumococcus, influenza bacillus and other bacteria, which as a rule occur only in advanced cases with cavity formation; there is rather the possibility that the unavoidable and severe reactions may in such cases afford opportunity for the extension of the secondary infection and lead to a worse condition. But these are the only cases in which direct harm can be caused by tuberculin. According to F.

**Kraus' Summary of Unfavourable Cases.** Kraus [258], these highly febrile forms with extensive inflammation and subsequent caseation are not likely to benefit from specific treatment. Also phthisis with broncho-pneumonia or pneumonia following measles or influenza, extending over an entire lobe, highly febrile but without sputum, often quickly deteriorate under tuberculin treatment. Equally unfavourable are those cases which are characterized by a hale and often plump appearance, but having diffused foci in both lungs; in such cases severe hæmorrhages and extension of the infection very often occur after tuberculin. We, too, strongly deprecate the attempt being made in this class of case, which is already practically hopeless.

**Extension of the Indication.** On the other hand, the indication for the use of tuberculin is no longer to be limited to the cases eligible for admission to a sanatorium. If the duration of treatment be prolonged and tuberculin be included in it, the selection of patients by the insurance companies will tend to widen considerably, a fact which our statistics have proved for years. Emphasis has already been laid on

**Limit of Curative Action of Tuberculin.** the fact that a certain reserve of strength and a certain degree of resistance are presupposed for an active immunization. It must also never be forgotten that even with good training in diagnostic methods there are considerable limitations to our knowledge of anatomical changes, that the pathological processes generally reach further than we are inclined to assume, that we are often dealing with cases which are more severe than we believe them to be. This is not unimportant when we come to judge our therapeutic measures, and to assess the measure of success possible and to estimate the success attained, especially in so protean and changeable a disease as pulmonary tuberculosis. These considerations will warn us against overestimating the curative power of



tuberculin, but will also help to prevent an underestimation of its value, even when sometimes the result of specific treatment does not come up to our expectations.

Definitely progressive forms of disease need not be considered for tuberculin treatment, nor is much to be expected in the case of advanced processes where much destruction of lung tissue has taken place. Recovery is only possible within the range which pathological anatomy shows to occur in the case of spontaneous curative processes. It is therefore advisable to have a clear idea of the latter; fibrous forms of the disease, even when widely affecting both lungs, may become stationary, and through scarring and contraction reach a complete cure. Localized softenings of even considerable area may be cast off and healing take place with formation of smooth-walled cavities which contract to a larger or smaller extent. Thus even advanced processes are capable of retrogressive change and complete scarring. Where the inflammatory process is so far advanced that retrogressive change is no longer possible, the disease must get the upper hand with or without tuberculin. But no other tissue of the human body is so fitted for contraction by cicatrization and for effective healing, after shedding even of fairly large necrotic areas, and for retaining its functions, as the lung. Where masses of tubercles disintegrate, this in itself admits the possibility that in their further destruction they may produce further damage, as the tubercle bacilli are not killed. This will be the case when they are not relatively quickly disposed of by the natural excretory methods of the organ in question. But for *pulmonary* tuberculosis these dangers are not great, for just such an organ as the lung is highly capable of getting rid of such products by the mechanism of its natural excretory channels. Nevertheless, there is need for great care, individualization and very exact control of the condition of the lungs in the specific treatment of the more advanced stages, where such dangers are greater than in slight infiltrations and smaller disseminated foci.

**Improvement  
where Recovery  
is Impossible.**

The value of a therapeutic agent is not exhausted with its absolute curative power. Hammer [259] has laid stress on this point with convincing clearness. If in the more severe and in the worst forms of pulmonary tuberculosis complete recovery is in the nature of things unattainable, improvement may yet be reached, and tuberculin has its place in the front rank of remedies for treating special symptoms. Dry cough disappears or loses its distressing character; sticky sputum, difficult to bring up, becomes more fluid and expectoration more easy; the painful



effort to bring up something by prolonged coughing ceases, as well as the associated vomiting, the patient regaining his peace and quiet; pleuritic pains are favourably affected by the greater ease of expectoration and the lessening of cough, also, more directly, symptoms such as headache, palpitation, dyspnoea, fever and night-sweats may be got rid of for a longer or shorter time; the appetite improves, tiredness and weakness vanish, bodily strength returns to some extent; at the same time the spirits improve, hope of recovery awakens, and the will to persevere in the treatment is strengthened. Since the mind reacts on the body, all these are factors of immeasurable importance in a disease of such chronicity and presenting such difficulties for the physician. The impression is unmistakable that the tuberculin-treated patients improved greatly in appearance, and that even in the severe and incurable cases the resistance of the body can be markedly raised. Such subjective improvement, which may be accompanied also by amelioration of symptoms, speaks loudest for the value of tuberculin when it is reached in out-patient practice in the absence of drug-treatment and under unfavourable conditions of life.

**Authors'  
Conclusions.**

Based on our own experience, we should say that, setting aside the severe incurable forms of consumption, especially cases of severe mixed infection with pyrexia, every uncomplicated case of pulmonary tuberculosis may be submitted to the mild method of tuberculin injection, avoiding as far as possible all reaction.

Other observers have drawn up a list of contra-indications to the use of tuberculin in treatment, to which, in view of their importance in practice, we must now turn our attention.

**Contra-indications:**

**(1) Fever;**

Under the term "fever" two different conditions are to be distinguished: that due to the settling of the streptococcus, pneumococcus, staphylococcus, influenza bacillus, or other bacterium in the diseased area, a condition known as mixed infection—secondary suppurative processes; and the pure toxic fever due to absorption of the toxins of the tubercle bacilli. The latter is by no means unsuited to tuberculin treatment. But even the mixed infections, on which tuberculin can exert no direct action, do not begin fully developed; with favourably situated and curable tubercular lesions the tuberculin exerts an indirect action on the fever, as the curative process renders the growth of the secondary bacteria more difficult and the culture medium on which they flourish is withdrawn. There need only be special care in giving the injections to employ minute doses, to let the rise of temperature, which generally occurs, completely fall to normal before repeating the in-



jection, and when necessary to reduce the dose and increase the interval. If the fever is increased by the repetition of the same dose, this must be reduced after a longer interval. If no advance is made by the repetition of small doses, a severe reaction with an increased dose may be the beginning of a permanent fall of temperature. The fall of temperature is very seldom acute. The temperature usually rises at first quite or nearly to its original height and only after repetition several times definitely begins to fall; in view of the severe reactions, the intervals should be increased to eight to ten days. This effect in reducing fever we have noticed more with the bacillary preparations, especially bacillary emulsion, than with old tuberculin preparations. From other quarters, too, tuberculin has often been recommended as a means of reducing fever, for example by Aufrecht, Denys, M. Elsässer, Gabrilowitsch, John, F. Krause, Philippi, Sahli, Schröder, C. Spengler, Turban. Which preparation is the most effective in reducing fever is a matter on which opinions are divided. Small and very small doses are usual in seeking to reduce fever. As in many other difficult situations, definite directions cannot here be given. The treatment of fever is most emphatically individual; the principle can only be stated or illustrated by an example. Personal study is necessary for the beginner and tuberculin treatment should first be tried on the slighter uncomplicated case, with good resisting power, before coming to the more severe and febrile forms, which often demand great patience both on the part of doctor and patient. Care must be again enjoined and the point emphasized that in tuberculin treatment nothing is gained by violence. The period of treatment may be lengthened by waiting, but no harm results. Employment of too large or too frequent doses leads to overloading with toxin, and this applies also to the treatment of pyrexia. We would just like to point out that the treatment of fever tested by us is in every detail the same as the final method of R. Koch, as may be seen from the publications of Jochmann [171] of the Rudolf Virchow Hospital.

We have been able definitely to reduce fever in the slight and intermediate grades in Stadium I and II by sufficiently prolonged treatment, in Stadium III only in the cases of more favourable prognosis in which the patients were able to return to work.

Chart 20 shows rapid loss of fever in a severe case of sub-acute caseous phthisis, with high to moderate fever of four months' duration.

Chart 21 is an example of gradual loss of fever in a chronic case of fibroid phthisis with slight febrile symptoms. Both



cases were treated with bacillary emulsion, the doses being at first small, but increased each time by one half of the preceding dose, without frequent or severe reactions taking place.

Chart 23 shows a more gradual loss of fever in a case of tuberculosis of the bronchial glands, with slight pulmonary tuberculosis, rapidly rising doses of sensitized bacillary emulsion being used. This patient was never confined to bed during the fever. We have found that cases with obstinate slight fever treated by tuberculin can be allowed out of bed much sooner than those not treated specifically, without increasing the fever or lowering the general condition in any way. Of course, careful observation and regular control of the body-weight are essential.

**(2) Debility ;** Debility is also no absolute bar to tuberculin treatment. The body, if its strength is much reduced, is not, it is true, capable of responding to the part assigned to it in the injection of tuberculin, the formation of antibodies. It is then generally a question of widespread tubercular changes. Where this is not the case and the specific changes offer prospect of recovery, then a bad condition of nutrition, great anæmia or general weakness is only a ground for double care in the employment of tuberculin. If, however, there is time to wait, it is highly advisable before beginning tuberculin treatment to improve the constitution by other therapeutic means, hyper-alimentation, improvement of the blood, &c. We have often been unable to wait and have begun at once with careful injections, employing at the same time all other therapeutic means as adjuvants. In so doing we have never had to suspend the injections on account of low vitality. Precisely under the influence of tuberculin the constitution obviously improved, appetite became better, weight increased, pulse slower and fuller, feeling of well-being and bodily vigour returned, and the composition of the blood became better to the naked eye. In any case tuberculin treatment is not excluded by a general condition of debility, poor nutrition, lack of appetite, dyspepsia from various causes, and the severer kind of anæmia, but a careful trial is permissible and generally successful. According to F. Kraus, even the so-called cachectic tuberculosis, with unfavourable general condition and appearance, often with but slight pulmonary signs, is extremely favourable for tuberculin treatment.

**Effect of  
Tuberculin on the  
Blood.**

Recent blood examinations are such as to strengthen reliance on treatment with tuberculin; the hæmoglobin content of the blood rises, red and white blood corpuscles increase in number, and, according to Arneth, hand in hand with



the increased dose of tuberculin goes an improvement of the neutrophile blood-picture, far greater than occurred in a parallel series of cases treated by other methods (Uhl, Deneke, Catoir, v. Bonsdorff, Franke). According to Bischoff, Botkin, Rille, and others, injections of tuberculin produce more or less definite leucocytosis and increase of the eosinophile cells, which Teichmüller considers to be of favourable prognosis. The careful and valuable work of Maryan Franke [260] deserves special consideration. He succeeded by prolonged injections of tuberculin of human origin into guinea-pigs and dogs in producing (1) an increase in the red blood corpuscles, and discovered the cause of this to lie in an increased production of these corpuscles in the erythroblastic tissue of the blood-forming organs, and (2) in establishing a polynuclear neutrophile hyperleucocytosis, especially as the result of a proliferation of the myeloid portion of the bone-marrow. According to his investigations, bovine tuberculin produces in the same animals a direct destructive effect on the red blood corpuscles and the granulated leucocytes in the bone-marrow, with increase of the lymphocytes and the simultaneous appearance of slight metaplasia of the bone-marrow. It would be valuable to know the results of these experiments on human beings, both as regards diagnosis and therapeutics; unfortunately very little has been done in this direction, and what little has been done is of no importance.

**(3) Tendency to  
Hæmorrhage;**

Tendency to hæmorrhage we do not regard in principle as a bar to tuberculin treatment, nor as an indication to stop it altogether. In cases of slight hæmorrhage the injections can be continued without interruption. A considerable hæmorrhage should, of course, be the occasion of a pause in the injections and of special care in increasing the dosage, so as not to run the risk of a reaction at this time. But it has never happened in our experience that a hæmoptysis during tuberculin treatment has, on persisting with the injections, recurred in such a way as to justify the deduction of a causal relation between them.

Moreover, relapses are of frequent occurrence in hæmorrhage of the lungs; yet although the number of our tuberculin patients who have suffered from previous hæmorrhage is high, relapses, in spite of the employment of the largest doses of tuberculin, are most rare. And since our total number of tuberculin patients has been large and it has been rather the severer cases that have been chosen for treatment, the rarity of hæmoptysis is in favour of the view that tuberculin does not increase the liability to it. To the rare exceptions may belong the breaking down of a



tubercle in the wall of a blood-vessel caused by the local reaction when the tubercle lies in the immediate neighbourhood of a cavity. But when, in the neighbourhood of a blood-vessel, a focus which is already bound to break down is softened by tuberculin, rendering possible the occurrence of an aneurysm and a rupture, this is merely part of the natural course of the local diseased process, which would have taken place in the same way if tuberculin had not been used. This is also the view of those with the widest experience in the treatment of tuberculosis and has recently been confirmed by numerous sanatorium reports and papers read before congresses, which confirm the harmlessness of tuberculin in hæmoptysis. By some tuberculin is even regarded as an agent for preventing hæmoptysis, the view evidently being that the local hyperæmia caused by the local reaction distributed over the diseased area draws the blood away from the ruptured vessel. Perhaps also the saturation of the hyperæmic tissue leads to a compression of the rent in the vessel and to better thrombus-formation. Grau's [261] experiments, too, are interesting and valuable, proving the increase in the coagulability of the blood after injections of tuberculin, which he explains as the result of the reaction of the organism to the introduction of foreign albumin. Thorner observed the tendency to hæmorrhage disappear under tuberculin treatment, Löwenstein and Kauffmann continued the injections in a great number of cases of recurring hæmorrhage and never noticed any harmful effect. Th. Curschmann has never seen frequent hæmorrhages during tuberculin treatment; on the contrary, patients who had previously often suffered from them were only exceptionally troubled by hæmoptyses during treatment. A. Schnoeller even considers habitual sufferers from hæmophilia good subjects for treatment with tuberculin. Kraemer's experiences go to show that patients treated with tuberculin are generally protected from the occurrence or repetition of hæmorrhage.

**(4) Morbus Cordis.** Abnormal conditions of the heart can only be regarded as a contra-indication to treatment with tuberculin when febrile reaction and toxic absorption cause a risk of disturbance of compensation and collapse. The danger may be met by the timely exhibition of powerful heart tonics, but loses its importance when the method of treatment is the mild one avoiding reactions. Valvular lesions are not common in the subjects of pulmonary tuberculosis. Lesions impeding the circulation through the lung make the occurrence of pulmonary tuberculosis more difficult or exclude it altogether; cases of existing pulmonary tuberculosis with accidental valvular



lesions have a bad prognosis and are unsuitable for tuberculin treatment; well-compensated lesions are no bar to the treatment. Degenerative processes in the heart-muscle and coronary vessels, as well as severe functional affections of the heart, demand great caution in the application of the method or giving it up altogether; numerically they are quite insignificant. In principle they are

(5) **Severe Organic Diseases.** contra-indicated to the same extent as other severe organic diseases, such as severe diabetes, many forms of nephritis, cirrhosis of the liver, &c., in which the prognosis is already bad. The mere presence of albumin in the urine, however, is in itself no contra-indication; each case must be considered on its merits

**Albuminuria.** and a careful test made where there is doubt. We have some experience of cases in which the passing of albumin and renal epithelium ceased under tuberculin treatment, but where the diagnosis of renal tuberculosis was by no means certain.

Peters (Davos) informs us that he holds neither chronic nephritis nor even diabetes to be a contra-indication; he has never had to suspend tuberculin treatment on account of these complications. In one case in which diabetes had existed for years with 7 per cent. of sugar in the urine in a patient with severe phthisis, the sugar completely disappeared.

(6) **Functional Nervous Disease.** Finally, among the contra-indications have been mentioned hysteria, with its varieties of neurasthenia and the severer forms of "nervousness," as well as epilepsy. With equally good reason all other functional neuroses—neuralgia, migraine, habitual headache, and the like—might have been included. On the basis of our own experience we can definitely state that there is no justification for this exclusion except in the case of the severer forms, when the hindrance is more on external grounds. There seems to us no logical reason for making the exclusion. A sanatorium for tubercular women affords material enough of this kind, and no special difficulties due to these complications have arisen, except those inherent to the conditions themselves. We may quote two cases of well-marked Graves' disease, in which not only the usual heart disturbances were present, but a number of other nervous symptoms (giddiness, headache, excitability, hysterical symptoms, tremor, affection of the sympathetic, and alteration of the secretions); in both of these tuberculin treatment could be carried to a successful finish with good influence on both diseases. Kraus also does not consider Graves' disease a contra-indication.



**Tuberculin in  
Pregnancy.**

There is only to add that, in common with Denys, Hammer, Petruschky, Scherer, Kalabin, and others, we have treated a considerable number of pregnant women with tuberculin; this is always well borne, with excellent results. In no case was pregnancy a drawback to the use of tuberculin. In this connection we may also mention that therapeutic tuberculin injections need not generally be suspended during menstruation, but that pre-, inter-, and post-menstrual rises of temperature must be noticed and recognized. Any increased tendency to reaction (as shown by v. Dungern, Hirschfeld, and Schenk to occur in animals) to certain subcutaneous injections, and which may also possibly be feared for tuberculin, we have never observed. On the contrary, Stern has just proved that the degree of reaction to the cutaneous test decreases towards the end of pregnancy. If, as Stern assumes, this phenomenon is due to a decrease of antibodies, which possibly explains the unfavourable influence of pregnancy on the disease, then tuberculin treatment is definitely indicated in pregnancy. The fear that a tuberculin reaction may cause abortion is groundless when the sexual organs are sound and the foetus healthy. Hammer and Petruschky even state that children born after a course of tuberculin were particularly strong and healthy, and also grew up so.

We have now alluded to the last ground sometimes given as an objection to tuberculin treatment and have, in so doing, limited to their necessary minimum the contra-indications in general. These the beginner will have to construe more widely and stringently than the practised clinician, a fact on which emphasis has already been laid.

**2.—TUBERCULOSIS OF THE RESPIRATORY TRACT.****Nose and  
Naso-pharynx.**

Tuberculin has been strongly recommended in tuberculosis of the nose and naso-pharynx (*e.g.*, by Onodi, Rosenberg, Schnitzler). Also lupus of the pituitary mucous membrane has been successfully treated with tuberculin by various authors. According to Wichmann, tuberculin alone has proved successful in the latter disease and deserves to be used in all suitable cases. In extensive infiltrations and tumours, especially in the cartilaginous nasal septum, operative measures must aid and prepare for specific treatment. The real domain of tuberculin, both in the nose as in the upper respiratory passages in general, is in ulcerative processes. As Blumenfeld [262] clearly explains, the



conditions for the healing action of tuberculin are specially favourable, as the necrotic parts of the tissue can be shed from the free surface. As for choice of cases and technique, with regard to the fact that pulmonary tuberculosis is generally present as a primary disease, the following description of the specific treatment of laryngeal tuberculosis will apply.

**Pulmonary Disease  
underlying  
Tuberculosis of  
Larynx.**

Wherever the task of treating pulmonary tuberculosis is undertaken, no matter on what lines, disease of the larynx demands and receives careful attention. But one has the impression that in the special treatment of laryngeal affections, that of the underlying pulmonary disease is often overlooked. And this is the more striking since tuberculosis of the larynx is only seldom primary, and in the vast majority of cases accompanied by an affection of the lung from which it has originated. It is not our object to go into the causes of this phenomenon; we only desire to point out that tuberculin is a means of filling up this patent gap. Not merely is it a rational proceeding to treat a complication of similar origin to the disease on the same principles as the disease itself, but a course of tuberculin will often limit the local treatment of the laryngeal disease.

The method of treatment is the same as for pulmonary disease and is, as a rule, subservient to the treatment of the latter. Selection of cases is therefore conditioned by the pulmonary and general condition. As in advanced cases of pulmonary tuberculosis, tuberculin cannot be expected to cure; this can still less be hoped for when there is

**Method  
Subserving  
thereto.**

any considerable disease in so important an organ as the larynx as a complication. The indication for the specific treatment of laryngeal tuberculosis is therefore similar to that for surgical treatment; it should not be attempted when and so long as the prognosis of the underlying pulmonary disease is unfavourable.

**Unsuitable  
Conditions.**

Ed. Meyer [263], who concurs with our views, considers the following local conditions unsuitable: very severe and pronounced laryngeal changes, accompanied by miliary, disseminated nodules; cases with symptoms of stenosis when stricture and danger of suffocation are not relieved by operation; cases with a strong tendency to breaking down of infiltrations, in which there is very probably a mixed infection. On the other hand, it is immaterial whether the tubercular changes take the form of infiltration, ulceration, or perichondritis, or a combination of these three forms.



Since the aim is in general to produce local reaction at the seat of disease and avoid general reaction, the possibility of control by means of the laryngoscope is an advantage to be made use of after each injection. In one respect—the possibility of inspection of the actual disease and of the effect of each injection—the treatment has a palpable advantage over that of pulmonary tuberculosis. But this is prejudiced because in the vast majority of cases the occurrence of a general reaction conditioned by the main disease regulates the treatment.

**Limit to  
Results.**

The effect of tuberculin on the larynx alone is difficult to judge, since the injections have always to be made with reference to the pulmonary condition. And in considering results it must be borne in mind that the prognosis of laryngeal tuberculosis is dependent on that of the underlying disease. Hence certain limits are set to the development of the curative action of tuberculin on the larynx. This action may be seen at its best when a severe laryngeal affection is associated with a slight pulmonary, when, therefore, the laryngeal mischief is the important one. A freer hand is then given in the production of local reactions, and if these are not well enough marked with the mild method of injection, resort may be had to more powerful reactions without being hindered by the pulmonary disease.

**Long Treatment  
Necessary.**

But as laryngeal tuberculosis almost always follows advanced pulmonary tuberculosis, the result of the tuberculin treatment is generally not immediately perceptible. For the incomparably larger mass of the diseased pulmonary tissue attracts to itself the whole or the greater part of the tuberculin injected by its avidity, especially in the first period of the treatment, and only allows it to act on the larynx after it has gradually become "saturated." To achieve real cures, therefore, in severe cases long treatment with tuberculin is necessary, in which large doses must be reached. This explains the good results obtained in the first era of tuberculin, quoted by good authorities. Therefore we are not astonished that those authors who now are in favour of small and the most minute doses at long intervals, or whose opinion is based on the short cures of the public sanatoria, have seen no results from tuberculin.

**Choice of  
Preparation;  
Satisfactory  
Results.**

Of the superiority of Koch's preparations there is no reliable and sufficient evidence; with all kinds of tuberculin satisfactory results have been attained. Even during the first tuberculin era, C. Gerhardt and



B. Fraenkel reported good curative effects, so that the latter has never ceased to use tuberculin. At the International Laryngeal and Rhinological Congress at Berlin in 1911, B. Fraenkel stated that he never had to suspend treatment with tuberculin and had had favourable results throughout. His last success was the cure of apical and laryngeal tuberculosis of a pregnant woman in the sixth month. At the same Congress, Grabower declared that since 1891 he had had consistent good results with tuberculin, especially in disease of the posterior wall and not too severe ulcerations. Moritz Schmidt used old tuberculin with good effect, especially in ulcerations and lupus of the larynx. After him P. Krause characterized it as a sin of omission not to make use of tuberculin. Recently Moritz points out the good effect of old tuberculin in laryngeal tuberculosis. Blumenfeld has seen torpid ulcers of long standing completely heal which had previously withstood all other local treatment—curetting, cauterization, lactic acid, &c. At the Association of Sanatorium Doctors, in 1911, Brecke vouched for the value of bacillary emulsion, even in cases complicated by fairly severe pulmonary disease. He emphasized the harmlessness of quite considerable focal reactions. In twelve cases in which the larynx was thus cured, the cure was maintained after many years; amongst them were teachers and priests who were able to pursue their calling. Willers, Polaczek, and v. Zander also report good results. From England, too, most satisfactory results are reported, for example, by Wilkinson, Williams, Waggett, Reik, Eyre, K. and S. v. Ruck. Wilkinson had such good results that he has abandoned all other methods. F. Krause prefers new tuberculin bacillary emulsion, Sahli and Dluski Béraneck's tuberculin. Ed. Meyer praises the good effect of sensitized tuberculin, in severe cases with the help of local treatment. At the Congress of German Throat Specialists, in 1911, he gave details of twenty-three cases [263] which proved a striking testimony for the value of the combined specific and endolaryngeal surgical treatment, for the most part results which he had never previously observed without tuberculin. These successes were the more noteworthy as they are obtained partly in out-patients living and working under unfavourable hygienic conditions. F. Kraus speaks highly of the action of sensitized bacillary emulsion in combination with local treatment in cases complicated by pulmonary tuberculosis, even when the conditions are very difficult (*e.g.*, diabetes), although the change for the better was often but temporary owing to the progressive general tuberculosis. Killian considers these very noteworthy results. F. Meyer [264] has



observed excellent results in laryngeal tuberculosis without extensive infiltration, and, in addition to old tuberculin, recommends albumose-free tuberculin, bacillary emulsion, and sensitized bacillary emulsion, the latter with subsequent old tuberculin treatment especially in severe cases. We have had great success with Koch's preparations, with bovine tuberculosis, and lately also with sensitized bacillary emulsion.

**Unfavourable  
Reports.**

Warnings, however, are not lacking against the use of tuberculin in laryngeal tuberculosis. Several authors are more or less opposed to it or sceptical (*e.g.*, Moeller, Besold and Gidionson, W. Neumann, Barwell, Lockard). Friedrich warns against its use. Even Kraemer, who is otherwise quite in agreement with us, is inclined to reject it. Schroeder, who not long since reported striking tuberculin cures with bacillary emulsion (out of eight cases six cures and one improvement), a little later got the impression that tuberculin is hardly any use and that in many cases it even led to the spreading of the process in the larynx and to the breaking down of the infiltrations. But a change of opinion in so short a time hardly speaks for trustworthy and reliable judgment.

**Authors'  
Favourable  
Experience.**

According to our experience, cases of laryngeal tuberculosis of slight and moderate severity will often be cured or vastly improved by sufficiently long and correct tuberculin treatment, often without the use of any astringent or disinfectant remedies.

Areas of redness and swelling, localized or diffused, often completely disappear.

**Treatment of  
Small  
Infiltrations;**

Small infiltrations are absorbed without leaving any sign; larger ones require longer time, according to their position. In typical infiltrations of the posterior wall, there frequently remain dense thickenings. When these are not too large, curette and cautery may be dispensed with. Sometimes these infiltrations break down, especially when this was on the point of happening spontaneously and absorption was no longer possible. But to deduce from this, as has been done, evidence of harm done by tuberculin, is merely an instance of thoughtless antagonism. The experienced clinician knows that the floor of the resulting ulcer cleans with remarkable rapidity, and is soon covered in by growth from the edges. In many cases of diffuse infiltrations which have obstinately resisted medical and surgical treatment, some measure of restoration will be obtained.



**of Ulceration ;** In cases of slight ulceration, too, we have increasingly given up all caustic remedies, the more experience we have had of the action of tuberculin. With dirty ulcers we are in the habit of insufflating first with disinfecting powder until the base is clean, and then beginning with the tuberculin injections or combining the two. Small ulcerations soon show a clean base, cast off sloughing edges, and rapidly become covered with epithelium. In the case of larger ulcers with deeply undermined edges, if the sloughs are not cast off with sufficient rapidity on continuing the treatment, resort may be had to the scissors or galvano-cautery, or to applications of lactic acid; by judicious combination striking results can be obtained in cases where the underlying disease is capable of substantial betterment.

**of Widespread Disease :** In cases of severe and widespread infiltration or other deep tubercular changes, especially perichondritic inflammation, **Perichondritis.** operative treatment cannot be avoided. But here treatment must often be limited to relief of symptoms on account of the serious nature of the underlying disease. Of tuberculin treatment in severe cases of this sort we have no personal experience. Such cases we should prefer to exclude from specific treatment, especially as they are generally accompanied by the graver forms of pulmonary disease and there is no reasonable expectation of improvement.

To sum up, recent experience has established—and we have contributed thereto by the publication of several cases of the cure of severe laryngeal disease—that with the help of tuberculin our results may be markedly improved, and that tuberculin deserves to be employed in the treatment of laryngeal affections more than has hitherto been the case. However, we have never recom-

**Combination with other Measures.** mended reliance upon tuberculin alone in the treatment of laryngeal tuberculosis. It is remarkable that this erroneous conception is current among our opponents. Owing to the enormous importance of testing the capabilities of tuberculin in the treatment of laryngeal tuberculosis in general practice, in which it is generally used too little, we have, indeed, for many years devoted ourselves quite specially to this study; nevertheless, our standpoint as regards laryngeal tuberculosis also is that general, local, and tuberculin treatment must be used to aid and assist each other just as we have recommended in pulmonary tuberculosis the combination of the best proved methods.



**Other Treatment.** Of fundamental importance also for the tuberculin treatment of laryngeal tuberculosis is rest of the larynx, and this is best obtained by forbidding unnecessary speech and, whenever possible, by absolute silence. Strict discipline in suppressing cough is a necessary adjuvant, irritation being lessened or abolished by the internal exhibition of narcotics and by inhalations.

With regard to the general treatment of laryngeal tuberculosis, the rules hold which we have given in describing the combination of tuberculin treatment with other methods for pulmonary tuberculosis.

**Prophylaxis of Laryngeal Tuberculosis.** Recently the demand has been made that greater attention should be paid to the prophylaxis of laryngeal complications in cases of pulmonary tuberculosis, and it is in tuberculin that we possess such a prophylactic remedy. By lessening or abolishing the cough irritation it prevents mechanical and inflammatory injury of the surface of the larynx, as well as the depositing of sputum in its lumen. But, above all, by its biological action it raises the resistance of the tissues of the larynx to infection.

The prophylactic value of tuberculin will be specially realized when the standpoint is taken that laryngeal tuberculosis is due to infectious contact, because tuberculin by making expectoration easier and loosening the sputum lessens the opportunities for infection by the collection of sputum in the larynx. Albrecht's recent experiments in rabbits point to the fact that laryngeal tuberculosis especially in its typical form is caused in the vast majority of cases by infectious contact with the sputum; that the tubercle bacilli, after superficial injury and loosening of the epithelium, pass through it into the submucous tissue. Hæmatogenous infection is certainly possible, but limited to a few atypical forms; experiments as to infection through the lymphatic vessels have given negative results; the question, therefore, as to the possibility of the occurrence must remain open.

**Use of Serum.** Weill reports a favourable and rapid action on slight and also moderately severe cases of laryngeal tuberculosis from the use of Marmorek's serum. According to Jereslaw the serum was tried in a series of cases of pulmonary tuberculosis in the sanatorium of Loslau, but the results were so unsatisfactory that it is no longer employed there. Yet laryngeal tuberculosis present at the same time was sometimes quite favourably influenced. The twelve cases reported are not very convincing as the results might be attributed to the general and local treatment which was used at the same time.



### 3.—TUBERCULOSIS OF THE DIGESTIVE ORGANS.

**Pharynx.** Michelson, v. Renvers and Rosenberg have obtained complete cures of pharyngeal tuberculosis by means of tuberculin. According to Blumenfeld, tuberculin is indicated in ulcers of the pars oralis which are of favourable prognosis, the patient possessing relatively good general condition, in which the pharyngeal tuberculosis is thus generally discovered at an early stage. Those cases of unfavourable prognosis are contra-indicated in which the disease is of a miliary nature and the process is one of rapid degeneration. Ed. Meyer and Lesser cured a case of rough, nodulated infiltration of the uvula and palatine arch in which miliary nodules were observed, by means of sensitized bacillary emulsion and simultaneous local surgical treatment, also the apical pulmonary and laryngeal disease present were healed and the necrosing infiltration of the cords partly cured. Schnitzler successfully treated tumours of the pharynx and naso-pharynx formed by numerous masses of tubercles by means of local tuberculin treatment; the tumours disintegrated, and there were formed fairly large and deep ulcers which showed an unmistakable healing tendency partly by beginning to skin over and cicatrize, and partly by the formation of clean and healthy granulations.

**Tonsils.** Trautmann has given details of tuberculin cures in tuberculosis of the tonsils; when there are febrile symptoms, increased swelling of the hyperplastic tonsils takes place, which after further injections recedes and gives place to healing, but only after some months' treatment.

**Lupus of Mouth and Pharyngeal Mucous Membrane.** Tuberculin has also proved of service in lupus of the mucous membrane of the mouth and pharynx. Improvement has been observed by Becker, Brieger, Burckhardt, Heymann, Hovell, Krause, and others. Heuck completely cured a case of extensive lupus of the soft palate, Kayser one of the gums, using large doses of tuberculin. According to A. Neisser, the tendency to heal in lupus of the mucous membrane of mouth and pharynx is recognizable earlier than in facial lupus of simultaneous occurrence, although complete cure generally requires subsequent light treatment.

**Stomach.** E. Fischer and Petruschky have cured tuberculosis of the stomach with tuberculin. With the lack of any other causal treatment it deserves a trial as long as the primary disease is not hopeless.



**Œsophagus,  
Intestines, Pancreas,  
and Liver.** Success with tuberculin in tuberculosis of other portions of the digestive tract have not yet been recorded. It seems probable that in tuberculosis of the œsophagus, intestines, pancreas and liver, almost always of unfavourable prognosis, specific treatment can hardly be of avail. However, it might be tried as an accessory remedy when the primary disease does not exclude improvement and the treatment has no general contra-indication. As a rule in intestinal tuberculosis, the advanced pulmonary disease stands in the way of a tuberculin cure.

#### 4.—TUBERCULOSIS OF THE UROGENITAL ORGANS.

The specific treatment of urogenital tuberculosis has only emerged from the experimental stage during the last few years since it has been more fully recognized in the province of other localizations of the disease. This is also partly because urogenital tuberculosis chiefly falls under the scope of operative surgery and gynæcology, and that a conservative standpoint has only lately begun to win ground, in which specific treatment certainly takes first place as an aid to hygienic-dietetic methods. Present reports of the value of tuberculin are very variable in the various localizations of urogenital tuberculosis. And further, isolated tuberculosis in most of the organs as a single clinical disease, especially in the male, does not occur. However, the results of specific treatment, as far as these have been recorded in the literature of the subject, will be described separately under the various organs with a common description for the urinary organs of both sexes.

**Urethra,  
Prostate, and  
Vesiculæ  
Seminales.**

There are no separate reports of the specific treatment of urethral tuberculosis. Also in tuberculosis of the prostate there are but few experiences recorded, such as those of von Hesse. We agree with the standpoint of Casper who, including this in the question of the specific treatment of tuberculosis of the vesiculæ seminales, advises a trial of tuberculin first of all, and at any rate before surgical measures as an aid to conservative treatment.

**Male Genital  
Glands.**

The value of tuberculin in tuberculosis of the male genital glands is a proved fact. In tuberculosis of the testicle, excellent results have been obtained by Lenzmann, Ullmann, Pogue, Kehl, E. R. W. Frank, and K. and S. von Ruck. Karo cured a tuber-



cular fistula of the testicle with tuberculin, which had been treated for some months with Marmorek's serum without avail. Jochmann had favourable results in three cases of tuberculosis of the epididymis.

**Bladder.** In tuberculosis of the bladder, which is always secondarily infected from the kidneys or genital glands, tuberculin is being increasingly recommended by many authorities. Jochmann had very favourable results in two cases, Pogue in four cases, and Hesse in one case. Birnbaum, in four cases, obtained one certain and one probable cure, and two were considerably improved. Schroeder cured one case and improved another. Roth was able to prove cystoscopically the healing of ulcers in the bladder after tuberculin treatment. Suter, on the other hand, in two cases of tuberculosis of the bladder after previous operation on the kidney, observed no *local* improvement; a third patient suffering from genital and bladder tuberculosis following nephrectomy died.

**Kidney.** The subject of the specific treatment of renal tuberculosis is a matter of considerable discussion, particularly with regard to the question of whether a case of unilateral tuberculosis must on principle be operated on or whether this may be postponed and specific treatment employed. The present state of opinion is as follows:—

**Opinions: of Israel;** Israel, while recognizing the valuable action of the remedy, demands extirpation of the kidney when only one is affected and the bladder healthy, reserving tuberculin treatment for cases of double affection, for after-treatment, or when operation was refused—a standpoint also taken up by Knorr.

**Casper;** Casper [265] demands operation whenever possible, especially in advanced tuberculosis of one kidney. Operation is contra-indicated in cases of pronounced general tuberculosis, simultaneous genital tuberculosis, and in cases where the second kidney's functions are no longer normal; here tuberculin treatment can be employed, which he has proved to be specially useful in tuberculosis of the bladder after the diseased kidney has been removed.

**Karo;** Karo [266] sums up his verdict by stating that Koch's old tuberculin often produces a complete cure in the initial stages of tuberculosis of the kidneys. Specific treatment in the early stage of the disease is also to be preferred because it is of a secondary nature and after successful nephrectomy the second kidney often becomes infected from the



primary focus (three personal observations in the course of one year). The great importance of the specific treatment lay in the fact that it not only cured the tubercular kidney but also the primary focus, and so prevented the infection of the other kidney. He had cured or radically improved twelve cases with tuberculin. According to Karo, tuberculin treatment is also indicated in all cases when both kidneys are diseased. Moreover, tuberculin treatment, after removal of the primarily diseased kidney by operation, assists the natural cure of the bladder and genital organs affected by tuberculosis.

**Mantoux;** Mantoux [267] expresses almost the same opinion, based on seventy cases of tuberculosis of the urinary apparatus collected from the literature. 33 per cent. were cured, 48 per cent. appreciably improved. Various kinds of tuberculin produced the same effect. The treatment must be strictly individual and reactions most carefully avoided. Simultaneous general and local treatment aids in effecting a cure.

**Kornfeld.** Kornfeld's work is also specially valuable. As a result of a general inquiry conducted by him, he considers the prognosis of tuberculosis of the kidneys to be most satisfactory and hopeful when the hygienic-dietetic treatment is combined with tuberculin treatment.

**Other Favourable Reports.** Leedham-Green has published three cases of cures in the initial stage of renal tuberculosis in children; Pedersen of clinical healing in two cases of tuberculosis of kidneys and bladder which remained free from symptoms one and two years respectively after treatment. Teissier observed tuberculin cure in a case of bilateral renal tuberculosis, Schultze considerable improvement in tuberculosis both of the kidneys and bladder. John Pardoe obtained favourable results without resorting to any other method of treatment; of twenty-one cases five were cured and four distinctly improved. Pielecke, Jochmann, Keersmaecker, Kneise and Heinemann also obtained satisfactory results; Prochownik cessation of all symptoms and general well-being of three patients for three to ten years. The experiences of the medical clinic at Giessen, too, which Hohlweg has recently published, are important. Four patients suffering from advanced bilateral disease with more or less severe symptoms in the bladder for whom operation was no longer possible were treated. In all these the subjective symptoms were almost suppressed, and a considerable objective improvement was made, while one was almost completely cured.



**Unfavourable Reports of Kummell, Kraemer, and Suter.** In contrast to these favourable experiences, Kummell could see no curative action of tuberculin in tuberculosis of the kidney. Therefore he recommends that no time should be wasted in tuberculosis of one kidney, but that there should be an operation. He would only permit of tuberculin treatment in children. He takes up this standpoint because in four cases which had been treated up to one and a half years with tuberculin, he found, partly on operation, partly *post mortem*, extensive tuberculosis of the kidneys. F. Kraemer also found in the extirpated kidney of a patient who had been treated for seven months with tuberculin, fresh tubercles, the formation of which had not been prevented by the tuberculin. Suter records a case in which increasing deterioration of the condition in spite of over a year's tuberculin compelled extirpation of the kidney, which brought about a cure. Unfortunately nothing definite is said as to the method of treatment, on which of course everything depends.

**Bachrach and Necker's Method.** Bachrach and Necker, in conjunction with Wildbolz, observed increase of weight and improvement of the general condition but no local healing action; they consider that the value of tuberculin treatment lies in the tox-immunity of the organism. Bachrach and Necker recommend a reactionless treatment for early cases, until there is an indication for nephrectomy, for tubercular cases in whom nephrectomy has been performed in which foci in the urogenital system or other organs remain, and also that it should be tried in inoperable cases in the absence of any more efficacious remedy.

The desirability of treatment with tuberculin *after* operation on the kidney receives general recognition.

**Lenhartz.** Lenhartz is particularly warm in his general recommendation of tuberculin for diseases of the urogenital apparatus. He claims that tuberculin treatment must precede surgical measures, as he has seen absolute healing with the former even in severe cases.

Fr. Müller and Stintzing have also quite recently expressed their general recognition of the value of tuberculin in the treatment of urogenital tuberculosis.

**Bevan and Philip.** At the International Congress on Tuberculosis in Washington, Bevan recommends the combination of surgery and tuberculin treatment. Philip recognizes the power of tuberculin as follows: Tuberculin can take the place of surgery:—



(1) In certain cases in which a topical diagnosis cannot be made with certainty, or when the result of the operation is either doubtful or fruitless.

(2) In a number of non-operable cases on, for example, extensive tuberculosis of the urinary and sexual organs, in which a radical operation is impossible.

**Lelongt's Recommendation.** Lelongt gives a general recommendation of tuberculin for all urogenital tuberculosis; he states that in many cases a cure is obtained, improvement is almost always seen, and with correct technique aggravation of the condition is a rare occurrence. It is specially indicated in vesical tuberculosis, in tuberculosis of the male genital organs, in bilateral and commencing unilateral renal tuberculosis, and in a recurrence of renal tuberculosis after extirpation of one kidney.

**Female Genital Organs.** The introductory notes to this chapter have a special significance in tuberculosis of the female genital system. Here the advocates of surgical and conservative methods are very definitely in opposition. It is natural that those who recommend radical operative measures are much more reserved towards the question of specific treatment than those who recommend conservative methods. In the former case the opinion is that the use of specific remedies is only permissible when operative gynæcology has reached the limit of its capacity. This assumes that specific treatment is not to be tried in cases of tuberculosis of the female genitals of favourable prognosis. It is, at any rate, certain that present ideas of the value of specific therapy in this branch of medicine are too limited. Advocates of the conservative method take up the standpoint based on their experience that conservative treatment holds out greater prospects of success the earlier it is combined with specific treatment. Thus Veit, for example, strongly recommends tuberculin, from the use of which he has seen far better results than from operative measures.

**Vagina.** The treatment of tuberculosis of the vagina, usually of a secondary nature, is regulated by the primary disease of the genital organs, on the extent and prognosis of which the result of the former depends. Where operation does not appear to be indicated, Veit states that the best general treatment is the hygienic-dietetic combined with tuberculin.

**Uterus.** In isolated tuberculosis of the uterus there are few reports of specific treatment. Seeligman gives a favourable verdict.



**Appendages.** In tuberculosis of the appendages reports are rather more numerous, and, as a rule, decidedly satisfactory. The following are the most important recorded in the literature of the subject, and are not confined to this localization alone, but also relate to disease of other genital organs usually combined with it.

Prochownik [138] reports great success with tuberculin in twenty-two cases of female genital tuberculosis, in which he obtained complete cure or a lengthy standstill (up to fifteen years). The larger tubercular tumours must be operated upon; in general, however, he is in favour of prolonged conservative treatment of a general nature combined with tuberculin. It should be specially noted that he never observed local relapse in his tuberculin cases.

Birnbaum [137] has treated four cases of tuberculosis of the appendages with tuberculin, in which he claims to have produced complete cure; in two cases there were no longer any objective symptoms, and in the other two the symptoms completely disappeared and the tangible objective condition spoke for a complete healing or standstill of the process. Therefore Birnbaum temporarily dispenses with laparotomy in tubercular disease of the appendages.

Seeligmann has had success in tubercular pyosalpinx. Kelly observed great improvement in several cases of genital tuberculosis. Fritsch also believes in specific treatment on the ground of his own observations. Schiller is in favour of a combination of operative and specific treatment in genital tuberculosis.

Further, while Busse had almost uniform success with the ambulant specific treatment of tuberculosis of the appendages, Zoeppritz considers its action unreliable for this disease in distinction to its regular healing influence on peritoneal tuberculosis.

Ziegenspeck recommends after-treatment with tuberculin following operation in genital tuberculosis. In this way he brought the trouble to a lasting standstill in tubercular pyosalpinx, in one case with advanced tuberculosis of the abdominal walls.

**Tuberculin in Tubercular Dysmenorrhœa.** In conclusion, attention must once more be drawn here to the excellent effect of tuberculin on the form of dysmenorrhœa caused by tubercular intoxication in manifest and latent tuberculosis, which we are able to confirm.

Recently Gräfenberg [268] has studied these disturbances in



detail at the Kiel University Women's Clinic. He reports very favourable results in out-patient cases of prolonged tuberculin treatment, under which not only the dysmenorrhœal but also other pelvic-peritoneal symptoms disappeared. He conceives primary dysmenorrhœa, which is often characterized by violent local reactions of the genital system as well as general reaction, to be inflammatory dysmenorrhœa in local or only latent genital tuberculosis. The results of tuberculin treatment are all the more important, as in many cases an operation, however trifling, may cause spreading of a latent form of genital tuberculosis (Gräfenberg, Poncet and Leriche, Prochownik); thus amongst Gräfenberg's cases there were several in which simple dilatation of the laminaria-tents for dysmenorrhœa resulted in acute genital and finally miliary tuberculosis.

#### Choice of Tuberculin.

In the treatment of male and female genital tuberculosis, no one specific remedy has proved itself superior; tuberculins, however, have proved more valuable than serum. According to Lenhartz, old tuberculin is preferable to new tuberculin. Veit strongly recommends the latter. Wright, Raw, Seeligmann, and John Pardoe use TR, Pedersen and Schröder Koch's bacillary emulsion. Birnbaum injects alternately new and old tuberculin, in ambulant practice only the latter. Jochmann begins with old tuberculin and completes the treatment with bacillary emulsion. Sahli reports very favourably on Béraneck's tuberculin, Le Clerc-Dandoy on Denys' tuberculin. Great improvements have been observed after treatment with Klebs' tuberculins, for instance, by Roerig in vesical tuberculosis and by Krüger in three cases of urogenital tuberculosis.

#### Serum.

With Marmorek's serum Schenker noted striking improvement in four cases of disease of bladder and kidney. Landau reports the appearance of several crater-shaped fistulæ covered with considerable granulations, which had arisen after operation in tubercular appendage disease, leading to a wound as big as a shilling in the abdominal wall, which defied all treatment. The condition improved sensibly under Marmorek's serum and the fistulæ healed up. On the other hand Karo [135] could not perceive any favourable action by the serum in any single case of urogenital tuberculosis, so that in the end he abandoned its use, all the more because in one case in immediate connection with it a case of miliary tuberculosis occurred which ended fatally. A tubercular fistula of the testicle, treated with Marmorek serum in vain for months, healed up smoothly under tuberculin.



## 5.—TUBERCULOSIS OF THE SEROUS MEMBRANES.

**Pleura.** Tuberculin treatment of the pleura is continuous with that of the lung. It is natural that the subject has no separate literature. Either (1) it is a case of so-called idiopathic pleurisy in which pulmonary tuberculosis is present in a latent form, in which case its etiology is only clear after the cessation of the acute inflammatory and febrile symptoms and the time for specific treatment of the tubercular pleurisy is late or past (as recent experience has shown that idiopathic pleurisy is followed in a large percentage of cases by pulmonary tuberculosis, in the future, specific treatment will be more frequently considered); or (2) pleurisy occurs as a complication in pulmonary tuberculosis already diagnosed. In such cases as long as the dry pleurisy is very painful or the dry and exudative form is accompanied by fever, specific treatment is not indicated. From these considerations it is evident that in tubercular pleurisy it will generally be reserved for after-treatment, for which purpose we have often found it valuable.

**Peritoneum.** The value of specific treatment in peritoneal tuberculosis is definitely established. Olshausen, Zweifel, Fritsch and others reported favourably in the first tuberculin era, Fritsch after previous laparotomy; lately Ganghofner, Grosz, Latham, Wright in children, Fr. Müller, Chalif, Alapy, Ziegenspeck, Kleinknecht in adults all testify to its efficacy. Sprengel obtained an extraordinarily successful result in a case of tuberculous peritoneal tuberculosis. Birnbaum [137] brought about healing in all of five cases with a considerable amount of ascitic fluid; of five cases of dry tubercular peritonitis he cured four. Zoeffpritz recommends tuberculin treatment in peritoneal tuberculosis on Birnbaum's method; of eighteen cases treated three to six years previously, fourteen were able to work (of which nine were completely healed), and four had died. Busse treated thirty women with old tuberculin under rigid precautions. These were cases of peritonitis with pyosalpinx, exudative peritonitis, diseases of the appendages, some of which had been operated upon and some without previous surgical treatment, dysmenorrhœa, and menorrhagia. Sixteen were cured, five improved, and eight remained unaffected; one patient was lost sight of. Simple laparotomy with subsequent old tuberculin treatment is also strongly recommended by the Breslau University Women's Clinic on the ground of results in thirty-six cases of peritoneal tuberculosis. Heimann [141], who records the details, attributes the very satisfactory results (54 per cent. cured after two



years' observation) not only to the simple drainage of the fluid, but chiefly to the tuberculin cure always commenced six to seven days after the operation. He quotes the results of his experiments on animals as further proof, in which he observed all the stages of the healing processes from the simple round cell infiltration to the true cicatrization round the former foci with simultaneous decrease of bacilli.

**Various  
Preparations Used.**

New tuberculin TR has been used by Raw and Warth, the latter at the same time performing laparotomy.

By subcutaneous injections of his own tuberculin, Rosenbach completely cured a case of exudative tuberculosis of the peritoneum. A second case with equally successful and rapid cure is recorded by H. Curschmann.

Schenker cured an apparently hopeless case of peritoneal tuberculosis with Marmorek's serum.

**Tubercular  
Meningitis.**

In the unfavourable prognosis of tubercular meningitis, little can be hoped for from specific treatment, and in most cases it is even contra-indicated. Uhthoff's report of a cure by specific treatment of ocular tuberculosis complicated by tubercular meningitis is all the more remarkable.

## 6.—TUBERCULOSIS OF THE EYE.

Tuberculin has brought about such triumphs in ophthalmic practice as to call increasing attention to specific treatment, and in this field a considerable contribution was made towards rescuing the reputation of tuberculin. The surprising cure of the severest forms of ocular tuberculosis, vision being retained without the assistance of any other therapeutic measure, is in fact so striking as to exert a healing effect also on the blindness of the opponents of tuberculin. Good results have been recorded for old tuberculin (Schoeler, Leber, Hummelsheim, Lindenmeyer, Emanuel and others), but new tuberculin deserves the preference. Small doses carefully graduated are employed, scrupulously avoiding anything like a severe reaction. The possibility of following in the eye the local reactions and every step of the curative process makes the employment of tuberculin specially easy and gives the clue to dosage, interval, maximal dose, and length of treatment. Krückmann, Reis and Kuhnt point out that it is just those cases of ocular tuberculosis which show distinct local reactions to very small doses of tuberculin, which derive great benefit from specific treatment.



**v. Hippel's  
Experience.**

A. v. Hippel [269], who has probably had as much experience as anyone of such treatment, recently recommends new tuberculin TR given by the following method. He begins the injections with a dose of 0.2 c.mm. and repeats the dose every other day, increasing by 0.2 c.mm. each time. From 2 c.mm. upwards he increases the dose each time by 2 c.mm., from 20 c.mm. upwards by 8 or 10 c.mm. as long as the temperature remains normal. If this is raised above 38° C. he injects the same dose two or three times running and only increases it again when no further general reaction appears. To go above 100 c.mm. v. Hippel considers superfluous, as he has succeeded in curing the severest cases of ocular tuberculosis with much smaller doses. He expressly warns against commencing treatment with too large doses, as in some cases of tubercular keratitis he observed the breaking down of corneal tissue situated over a tubercular nodule and the formation of an ulcer due to a local reaction of too great severity; it should be added, however, that these ulcers soon healed after application of a fomentation. v. Hippel's experience is that to prevent relapse the injections must be continued until all nodules are replaced by scar tissue, the swelling and vascularization of the iris have returned to normal, and precipitations on the posterior surface of the cornea as well as vitreous opacities have disappeared. To obtain permanent cure in the severest cases a period of six months or more is required.

**Use of Bacillary  
Emulsion.**

As in some cases, in spite of rapid healing, relapses occur later, v. Hippel, at Koch's suggestion, commenced using bacillary emulsion in 1906. The results obtained were similar to those of TR. But v. Hippel now gives the preference to bacillary emulsion, because according to his experiences up to the present it is distinctly less likely to be followed by relapses than TR (see Davids, p. 254). The method is exactly the same as with TR, beginning with 0.2 c.mm. and reaching a maximum of 200 c.mm.; the method is in general the same as that used for many years in the Göttingen University Eye Hospital.

**Results of  
Other Observers:  
Conjunctiva;**

Eyre, v. Hippel, Masing, Saathoff, Schwarz, Griffith, and Vossius report cures of tuberculosis of the conjunctiva. The value of tuberculin treatment in eczematous conjunctivitis is generally recognized; Tionen has recently reported successful results in fifty cases.



**Cornea;** Cases of corneal tuberculosis were cured by Busse, Dodd, Emanuel, Erdmann, v. Hippel, Laas, Lichtenstein, Rohmer, Saathoff, Schoeler, Ullmann and Wilder.

**Sclerotic.** v. Hippel and Brandenburg report cures in tuberculosis of the sclerotic, whilst Schoeler and Busse also saw good results in tubercular scleritis and episcleritis. Reis, with a few injections of old tuberculin, cured several cases of the so-called "tuberculoma of the bulbar conjunctiva," which is situated in the neighbourhood of the corneal margin, and, according to this author, hardly ever takes its origin from the conjunctiva but from the superficial coat of the sclerotic.

**Iris and Ciliary Body.** The conditions for healing are specially favourable in the vascular tissue of iris and ciliary body, a fact confirmed by the experience of M. Elsässer, Falkenberg, Handmann, Halben, Sattler, Reunert, v. Hippel, Bull, Stock, Lichtenstein, Kraemer, Schultz-Zehden, Brown, Bulson, Busse, Gamble, Vossius, and others. We, too, can report very favourable results. Augstein cured a case of severe tubercular iritis, in which the question of enucleation had been raised, with retention of vision. D'Alessandro published the account of a case exactly similar. Cramer obtained striking results in two cases of severe serous iritis (one of them after iridectomy for glaucoma), in a case of severe iridocyclitis with diffuse sclerosing keratitis and vitreous opacities, as well as in a patient with two isolated iridic tubercles complicated with a large infiltration in the sclerotic.

**Choroid.** Diem and Stock specially recommend tuberculin in tuberculosis of the choroid. Schoeler, with an exceptionally large experience, attained for the most part substantial improvement in twenty-nine cases. Cramer observed the cure of a large isolated tubercle in the choroid with heavy deposits on the cornea. Lubowski reports a similar case. Axenfeld, too, has seen cures of tubercle in the choroid. Emanuel records the favourable course of a case of choroiditis centralis with severe myopia. Busse's good results with TR include four cases of choroiditis.

**Vitreous Humour, Retina, and Optic Nerves.** The efficacy of tuberculin has also been proved in primary and secondary tuberculosis of the vitreous humour, retina and optic nerves, the etiology of which has only in recent times been investigated and this largely with the help of tuberculin. There are many records in the literature (*e.g.*,



from Schoeler and Igersheimer) of complete and permanent clarification of the vitreous humour with restoration of good eyesight after opacity and hæmorrhage. Amongst others, Augstein, Heerfordt, Igersheimer, Pick, Scheuermann, Schnaudigel, and Schoeler have obtained a definite healing action in tubercular retinitis, neuritis optica, papillitis, and retrobulbar neuritis. Many other notable results have been recorded in individual cases by a large number of other observers.

**Further  
Favourable  
Results.**

Favourable results in cases, some of them almost hopeless, are further recorded by Axenfeld, Berry, Dor, Erdmann, Franke, Groenouw, Hayashi, Fr. Müller, zur Nedden, Purtscher, Reuchlin, Schleich, Schoeler, Schumacher, Stargardt, Tillmann, Wolfram, Zimmermann, and others. In the Ophthalmic Clinic at Tübingen, too, new tuberculin is extensively used on account of the favourable, in part excellent results obtained. Augstein [121] has recently reported numerous favourable and rapid healing processes in severe cases not yielding to other treatment of parenchymatous keratitis, ulceration of the cornea, iridochoroiditis, with sympathetic affection of the sclerotic, choroiditic exudation with hæmorrhage, and iridocyclochoroiditis with turbidity of the vitreous humour.

The results obtained by Rémy Tardieu in twelve very obstinate cases of varied forms of tubercular affections of the eye in which the usual specific treatment failed are equally favourable. He noticed during the treatment simultaneous improvement in swellings of the glands, discharge from the ear, obstinate chronic rhinitis, facial lupus, and tubercular periostitis. He used a tuberculin from the Pasteur Institute.

**v. Hippel's  
Conclusions.**

v. Hippel (1904) is enthusiastic over the value of tuberculin on the basis of his excellent results with it. He was successful in curing the severest forms of tubercular disease of the eye, including several in which blindness had already occurred. His series includes twenty-three cases of tuberculosis of the iris, ciliary body and cornea, one of the sclerotic and three of the conjunctiva. After eliminating thirteen cases of cure which he considers not quite conclusive, there remain ten cases which were cured, and remained so for a period of nine and a half years. His conclusions, giving, as they do the general sense of his writings, may be quoted here: "On the basis of the facts recorded by myself I consider it proved that we possess in tuberculin TR a remedy which, rightly employed, can permanently cure the severest tubercular disease of the eye with



retention of vision. Based on this fact it becomes our duty, not, as often in bygone days, to enucleate such eyes without more ado, but first of all to attempt to combat the disease with the weapons which we owe to R. Koch. And we can do this with the less hesitation as experience has shown that in tubercular disease of the eye the exhibition of small doses of tuberculin, such as we are now in the habit of giving, has never produced any harmful result on the patient's general health, whereas, in a number of cases after enucleation, death occurred from meningitis. Time alone will decide whether by this treatment all tubercular eyes can be saved; the disease is so rare that the clinical material of a single individual is not enough to make certain. But even if only a considerable proportion are saved—and my results are sufficient to establish this—we can still chronicle a refreshing advance in therapeutics, made possible for us by the genius of Robert Koch alone.”

In 1905 v. Hippel records twelve further successful cases by his method, and again recommends the treatment with small doses over a long period of time.

**Superior Value of  
Bacillary  
Emulsion.**

Among the latest reports of the success of tuberculin in tuberculosis of the eye are those of Davids [270] from the Göttingen University Ophthalmic Clinic, emphasizing the superior curative effect of bacillary emulsion, which he considers specially protective against relapses. The preparation did not fail in any of the ten cases treated. In various forms of keratitis the cornea cleared noticeably. In all cases of tuberculosis of the iris the tubercles disappeared quickly, even when at first they had shown a tendency to multiply and increase. In the same way pupillary exudation subsided in a striking manner, the vitreous humour cleared and sclerotic tubercles subsided. Finally bacillary emulsion was also effective in conjunctival tuberculosis.

In other quarters, too, bacillary emulsion is preferred. Thus Scheuermann [271], from striking results in twenty-five cases in the Charlotte Sanatorium for Diseases of the Eye in Stuttgart, cannot recommend it too highly. The most striking cure was that of two solitary tubercles of the retina, choroid membrane, and optic disc, which would certainly have resulted in loss of the eye; with the exception of a slight diminution of the field of vision, the eye became quite normal.

Bacillary emulsion proved just as successful, according to Pick, in a case of severe tuberculosis of the eyeball, which had attacked extensively the conjunctiva of the ball, the cornea, the iris and the episclerotic, and had led to clouding of the vitreous



humour and severe neuritis optica. Uhthoff recommends it in specific tubercular growths in the iris and uveal tract; Jung gives it an unreserved recommendation. Horniker completely cured a very advanced case of tuberculosis of the iris.

**Schnaudigel.**

Schnaudigel [272] treated ninety-five cases of the most diverse forms of tuberculosis of the eye with good, often with brilliant results. The cases were divided among the different parts of the eye in the following way: Phlyctenular keratitis, 16; severe keratitis with ulceration, pannus and suppurating infiltrations, 30; quite torpid, recurrent inflammation of the cornea in childhood and in the second decennium, 3; serous iritis, 6; creeping plastic iritis with disease of the uvea and keratosclerosis, 27; uveitis with detachment of retina, 2; central and disseminated choroiditis, 4; diffuse choroiditis, 2; episcleritis, 2; optic neuritis, 1; retrobulbar neuritis with affection of the sphenoidal sinus, 2.

**v. Herrenschwand.**

v. Herrenschwand's [273] results are equally favourable. He secured far-reaching improvement, for the most part, even cure in twelve cases of parenchymatous keratitis, thirteen of phlyctenular conjunctivitis of the cornea; one of scleritis; seven of iritis, and six of disseminated choroiditis.

**Jusélius.**

Jusélius gives details of thirteen cases of active ocular tuberculosis (iritis, keratitis, choroiditis, &c.), all of which were cured.

**Schoeler's Success**

**with**

**Old Tuberculin.**

One of the latest publications which deserves mention on account of the large material of 170 cases, is that of F. Schoeler [124], of the Schoeler Ophthalmic Clinic, in Berlin. It is specially noteworthy that the results are achieved with old tuberculin. Schoeler reports on the remarkable effect of tuberculin in superficial and parenchymatous keratitis, iritis, choroiditis, scleritis, and episcleritis, vitreous opacity and recurrent vitreous hæmorrhage on a tubercular basis, also in retrobulbar neuritis of a tubercular nature. His experiences may be summarized as follows: The use of old tuberculin is strongly to be advised in suitable cases, in conjunction with the other known remedies. It aids them and increases the receptivity and tolerance of the eyes for other remedies. In some cases it has been effective in saving the eye. The dosage must be chosen so as to cause slight increases of temperature of a few tenths of a degree. Local reactions always pass off harmlessly without leaving any trouble behind. The tuberculin cure is a lengthy one and must be continued till no signs of disease are present, or until even with a rapid increase



of the dose no rise in temperature occurs. Maximum dose, 500 c.mm. Relapses sometimes occur, but less frequently than without tuberculin.

**Heine.**

Heine [120] bases his judgment on 125 cases in which there was unmistakably a favourable effect in one half, absent in the other half. There were eleven relapses after completion of treatment, three during suspension of treatment. The earlier the cure was commenced, the better was the result. On the ground of the success attained and the improvement in body-weight and the subjective condition of the patients, he considers tuberculin a very efficacious remedy.

**Gerok :**

**Old Tuberculin.**

Gerok's results in twenty-five cases were satisfactory and some quite surprisingly successful. Ten cases of iridocyclitis gave uniformly satisfactory results. Also cases of scleritis, iritis and choroiditis disseminata were favourably influenced, keratitis parenchymatosa less. A case of cerebral tumour with choked optic disc was healed and remained so during three years' observation. Old tuberculin proved the best preparation, very small doses being used and febrile and local reactions avoided as far as possible.

**Leber.**

Recently Leber has also expressed his opinion that old tuberculin is equal to the bacillary preparations in therapeutic efficiency, that its use has a theoretical foundation in the local character of ocular diseases, that it is less likely to cause toxic injury to the eye and deserves preference as it is easier to apply.

**Weeks.**

Weeks, as a result of inquiries of 102 North American oculists, informed the International Medical Congress in Budapest, in 1909, that the results obtained in tuberculosis of the eye by tuberculin were described on all sides as satisfactory. The preparations used were original old tuberculin, new tuberculin TR, and best of all, bacillary emulsion, according to v. Hippel's prescription.

**Junius'**

**Recommendation  
of Béranek's  
Tuberculin.**

The special recommendation by Junius of Béranek's tuberculin in tuberculosis of the eye, based on purely theoretical grounds, without any personal experience, seems to us not only unjustified, but also superfluous at the present time, in view of the brilliant results with Koch's preparations of tuberculin and the universally accepted and thoroughly tested method of v. Hippel. The value of Béranek's tuberculin in itself is not disputed. According to Fleischer, it has been used amongst other preparations and, com-



bined with clinical treatment, used for a sufficient length of time and with great care, gives results equally as good as other tuberculins.

**Use of Marmorek's Serum.** With Marmorek's serum Ullmann obtained excellent results in twenty cases of scrofulous disease of the cornea, mostly in children. He emphasizes the necessity of early treatment. Verrey also had a favourable result from the rectal administration of serum in a patient suffering from corneal tuberculosis with pannus, also from tuberculosis of the bones. The value of the serum is also confirmed by Schwartz, disputed by Bock.

## 7.—TUBERCULOSIS OF THE EAR.

In otological text-books the therapeutic use of tuberculin in tubercular affections of the ear is either not mentioned at all or adversely criticized, the reason probably being that tuberculin has been very little used in tuberculosis of the ear. All the more valuable, therefore, are the experiences of Voss [275], who, at the Scientific Congress in the Municipal Hospital at Frankfurt-on-the-Maine, introduced a patient who had been cured by systematic injections of bacillary emulsion of a chronic suppuration of the middle ear on both sides, with serious defects in the tympanic membrane and an infiltration on the left side with fibrinous exudation in the region of the promontory; other methods had long been tried without avail. Voss considers such cases specially suited for specific treatment, and thinks that chronic suppurations of the middle ear can be cured by means of tuberculin. Cipes records another case of cure of tubercular disease of both ears by combined tuberculin and local treatment.

In acute tuberculosis of the middle ear and of the mastoid process he would, however, advise the greatest caution, in contrast to Lebram, who has observed a curative effect from tuberculin even in these acute processes.

## 8.—TUBERCULOSIS OF THE SKIN.

**History of Lupus Treatment.** The treatment of tuberculosis of the skin and especially of lupus has undergone many vicissitudes. As long as it belonged to the sphere of internal medicine the results were by no means satisfactory. With the rise of dermatology to a separate place, progress began. The next stage, a transition to the surgical, was to destroy lupus nodules by scarifying or by means of the electric cautery or the sharp spoon. The surgeon finally set himself the



task of the radical removal of the diseased parts. When the cases chosen are suitable, excellent results are attained in this way, but the method has its limitations, as, for instance, in lupus of the mucous surfaces, especially of the nose, and in disease processes not accessible to complete extirpation; and, finally, where the lack of bodily strength bars the way. A further advance in the treatment of lupus was made by the introduction of Finsen's method, by Röntgen rays, and radium. To radium treatment the objection has been raised that it is difficult to limit the action of the rays. The Finsen reaction is easy to estimate, but the deeper the lupus tissue extends into the subcutaneous layer and the greater its extent the less is the prospect of success, and this is still further compromised by the presence of extensive scarring from previous unsuitable treatment. In extensive superficial processes, and those combined with disease of a mucous surface, Holländer's hot air treatment has shown itself of service. Of the latest methods of treatment—the internal exhibition of sodium iodide and the simultaneous use of ozone or hydrogen peroxide (Pfannenstill) and Nagelschmidt's diathermal treatment—there are at present insufficient records; to all appearances they are further advances.

#### Local and General Treatment.

In addition to the local treatment of tubercular skin affections, the general treatment of the organism as a whole plays a considerable part. Tuberculin is an accessory to general and etiological-specific treatment. Even in the first tuberculin era striking cures were recorded; but with the modern advances in dermatology, tuberculin was undeservedly thrown into the background, whence it is only recently emerging to be increasingly used in the most varied forms of tuberculosis of the skin and mucous membrane.

#### Lichen Scrofulosorum, Acne Cachecticorum, Scrofuloderma and Erythema Induratum.

Great success has attended the specific treatment of lichen scrofulosorum, Klingmüller at the Breslau Dermatological Clinic reporting cures. Many authors record a favourable influence on acne cachecticorum and some a cure. Thörner's results in scrofuloderma are satisfactory. Thibierge and Weissenbach, in ambulant practice, cured five cases of erythema induratum with increasing doses of various tuberculins without any accessory general treatment. Whitfield, Jeanselme, and Choralier confirm its curative effect.

#### Lupus.

There are naturally many more records of experiences in the treatment of lupus. Its



many-sided nature explains the fact that the results in all its forms and in all cases are not equally favourable. Between the use of old and new tuberculin no essential differences have been proved. From the very rich literature of the subject we can only quote the names of some who have recorded improvements following specific treatment: Adler, Balzer, Beck, Bieck, Bukowsky, Bussenius, Brocq, Browker, Campana, Cossmann, Crocker, Darier, Delbanco, Doutrelepont, Dressler, Faure, Gerber, Gross, Gunson, Heermann, Heron, Jadassohn, Jesionek, Kernig, Krzysztalowicz, Lassar, Leredde, Lesser, Little, Litzner, Mayer, Maynard, Medowikow, Morris, Pernet, Porges, Prang, Roberts, Seeligmann, Sternthal, Wälsch, Western, and Wright.

**Local Tuberculin  
Application.**

Many authors have tried the local application of old tuberculin in various forms in the treatment of lupus. Blaschko, Crocker and others have injected tuberculin dilutions into the lupoid tissue to promote local reactions with small doses and avoid general reactions. On the same principle Verge recommended a 5 per cent. tuberculin ointment. Unna successfully used inunction of a "tuberculin soap" (*sapo unguinosus* with 5 to 20 per cent. tuberculin) for lupus, with the idea of setting free autotuberculin by massage, and rendering it active. Blaschko and Hallopeau used tuberculin fomentations. Neumann scarified the lupoid surface and impregnated it with tuberculin. Ohler recommends the painting of tubercular ulcerations with tuberculin, by which means Schnitzler also observed disintegration and healing in tumours of the nasopharynx. Nagelschmidt has employed the production of a v. Pirquet papule in the local focus when ulceration varying in extent and depth almost always took place and in some cases led to clinical healing of the tubercular skin focus although only within a few millimetres radius.

**Subcutaneous  
Injection  
Preferable.**

All these methods have found but few followers. In tuberculin treatment of lupus, as elsewhere, the subcutaneous method has proved its superiority as the great majority of the above authors bear witness. Of other noteworthy results the following must be mentioned: Raw has treated 100 cases of lupus with old tuberculin, the great majority of which showed improvement. Jochmann's reports are also favourable.

**Jochmann.** "Patients, who had been treated locally with every remedy without success, made good progress under treatment with tuberculin. In other cases we had the impression that after distinct improvement at first, later a standstill occurred. Tuberculin treatment is specially



called for in cases in which other *local* remedies—pyrogallic acid, the Finsen treatment, or Röntgen rays—cannot penetrate, such as processes which attack the mucous membrane of the nose.” In his statement at the third session of the lupus section of the

**Wichmann.** German Central Committee for the Prevention of Consumption, Wichmann describes tuberculin as follows: “Although no sovereign remedy, it is a very valuable accessory and often an indispensable factor in the treatment of lupus.”

**Choice of Tuberculin.** As we have already mentioned, no one tuberculin has shown any marked superiority in the treatment of the disease. Sahli here, too, prefers Béranek's tuberculin, Rosenbach his own preparation. The authors have published reports of various cases successfully treated with old, new and bovine tuberculins. The efficacy of bovine preparations is specially emphasized by some authors who are inclined to draw conclusions from their action as to the etiology of lupus; thus Jochmann and Möllers recommend bovine tuberculin in all cases where the human preparation has no effect.

**Combination of Tuberculin with other Methods of Treatment.** The existing results suffice, at any rate, to direct further attention to the treatment of lupus with tuberculin. The sovereign modern remedies for lupus, as we have seen, have their contra-indications and limitations, especially in lupus of the mucous membrane. But there is no reason why tuberculin should fail here. We have emphasized this for years, and are gratified to find that Wichmann has recently recommended tuberculin as the most valuable remedy for lupus of the mucous membrane. Reports (for example from A. Neisser and F. Becker) exist which show that lupus of the mucous membrane of the nose, mouth, and throat were healed more rapidly and easily than the lupus of the facial skin, present at the same time. B. Fränkel, too, a short time ago gave a detailed description of the cure of a case of extensive lupus of the gums with a small primary focus in the nasal septum by large tuberculin doses. A careful study of the experience of the last decade will inevitably lead to assuring the place of tuberculin in the treatment of lupus in combination with the other well-proved remedies. Senger considers that no other treatment has so good an effect on lupus as the inunction of tuberculin ointment with vasenol in 3 to 10 per cent. concentration, in conjunction with Röntgen rays. Further, Wichmann, who has recorded lasting cures of severe cases of lupus of skin and mucous membrane, has



observed that tuberculin only displays its full curative value when the diseased tissue is previously rendered plethoric, *e.g.*, by weak Röntgen-ray treatment. And according to the experience of the Rostock Dermatological Clinic, old tuberculin, in combination with other methods, has proved its value, especially in open lupus, in destroying the tubercular tissue.

"The exciting cause of the disease seems to be enticed from the body and given out by exudation, and is then destroyed by pyrogallic acid" (Wolters).

The justice of our claim has been lately acknowledged by dermatologists, for instance by A. Neisser, Doutrelepon, Scholtz, Blaschko and Wichmann. A. Neisser, in contradistinction to Doutrelepon, has not observed pure tuberculin cures, but he considers tuberculin quite an indispensable *aid* in the treatment of lupus.

"Especially cases with large, swollen infiltrations and all infiltration of the mucous membrane of the mouth are treated by us with tuberculin, always by slowly increasing doses, but large enough to produce local reactions. In this way thick, swollen infiltrations become flat and smooth surfaces, in which the lupus foci are easily recognizable and amenable to further treatment with light" (A. Neisser).

We need the assistance of tuberculin in the treatment of lupus all the more as in a fairly high percentage of cases tuberculosis of the skin is combined with other internal tubercular disease, especially of the lung. And precisely on this account specific treatment is in place.

#### Importance of the Tuberculin Reaction.

Heuck also, who confirms the good effect of tuberculin on lupus, emphasizes the importance of the tuberculin reaction in recognizing the limits of the diseased and healthy tissue. These experiences agree with those of A. Neisser, who for years has utilized the local tuberculin reaction both for purposes of excision and for subsequent testing of the cure.

### 9.—TUBERCULOSIS OF GLANDS, BONE, AND JOINTS.

#### Operative or Conservative Treatment.

Tuberculin has been but little tried in the great region of surgical tuberculosis. When removal of the disease by surgical measures is possible, radical operation has always obtained the preference. But recently there has been a reversion to more conservative treatment, due in no small degree to Bier's pioneer work. But hyperæmia also plays the principal rôle as



curative agent in tuberculin, and the two methods have this in common in their fundamental action. We here stand only at the beginning of things, but, if the signs do not deceive, conservative therapy in combination with specific treatment is destined increasingly to limit surgical measures, to assist in many cases, and in some to replace them. This view, which has always been emphasized by the authors, has lately been accepted by surgeons of authority: Wilms [127], who has observed the greatest successes in the specific treatment of the fungoid form of surgical tuberculosis, considers the tuberculin cure not only appropriate for these cases, but absolutely essential, as a means of strengthening the body against the tubercular infection and especially of protecting it against relapse after removal of the fungoid focus. "The surgeon who rejects tuberculin therapy loses thereby a very efficacious remedy which I consider more valuable than iodoform, glycerine, stasis, &c., and which can only be compared with Röntgen treatment. I am convinced that the conservative treatment of tuberculosis, in distinction to the surgical methods still generally practised, will gain ground year by year." At the Karlsruhe Scientific Association, in 1911, at which Wilms put forward this standpoint, Czerny also declared his faith in tuberculin.

It is well known that a large percentage of cases of surgical tuberculosis, after being cured of their local affection, ultimately die of pulmonary or other internal tubercular disease. And there can no longer be any doubt that a systematic testing of the susceptibility to tuberculin, and if necessary a course of treatment with it, will immensely improve the results in the whole group of surgical tuberculosis; and not merely this, but prevent the outbreak later of a focus of tuberculosis localized in some other part, which, after long being latent, might sooner or later lead to a fatal attack. We owe it specially to Kraemer to have repeatedly and urgently emphasized this and established its correctness beyond dispute.

**Results :  
in Glandular  
Tuberculosis.**

In cases of glandular tuberculosis, Petruschky, where the disease was closed, obtained 100 per cent. of cures with old tuberculin. Krämer reports just as favourably; he considers tuberculin treatment in the case of children not only as the most important curative agent in glandular tuberculosis, which is usually in the foreground, but also for the extermination of tuberculosis in general. Tuberculosis of the bronchial glands, too, in children and adults, is, according to his experience, a specially favourable object for tuberculin treatment, all the more because a large number of forms of manifest tuber-



culosis proceed from it. v. Starck also observed after the use of old tuberculin in tuberculosis of the bronchial glands of children a strikingly good subjective condition, which was always followed by objective improvement. Rohmer proved a tendency to anatomical healing in the form of proliferation of the connective tissue and encapsulation of the bronchial glands in three children under 2 years of age, who died of other complications.

Peiper, at one time an opponent of specific treatment, has observed very satisfactory results in the glandular tuberculosis of children from the employment of minimal doses of old tuberculin. The same favourable opinion is held by Jochmann, Scherer, Aronade, Ullmann, Dumas, Lawson, Raw, Stoll, K. and S. v. Ruck, Hawes, and Floyd. Latham reports prompt results in anæmic and febrile children with glandular tuberculosis; he emphasizes the necessity of lengthy treatment, which must be prolonged after improvement has taken place. Heubner states that the immediate result of careful tuberculin treatment in glandular tuberculosis of young children is unmistakable as far as the improvement of the general condition and the scrofulous symptoms are concerned. Baginsky also recently recommended careful treatment with tuberculin. Pogue obtained very satisfactory results in ten cases of glandular tuberculosis with the formation of fistulæ. Guinard, in his cases, always observed softening and breaking down of the glands.

**Dautwiz.** Dautwiz [276] made an important contribution to the curative influence of tuberculin in latent endothoracic glandular tuberculosis in children. According to his wide experience it undoubtedly effects more in conjunction with hygienic-dietetic treatment than the latter does alone, more also than the sea-bath treatment (previously the most efficacious), even when this is repeated every year for three to four months. The superiority of tuberculin treatment is seen in the children recovering more quickly, more regularly and without relapses, losing their subfebrile and febrile temperature as well as the sternocostal and spinal tenderness, and proving themselves much more capable of resistance on their return to less favourable conditions of life. Dautwiz considers the most important point is the proof of the effect of tuberculin treatment on the endothoracic glands; he considers the principal effect of tuberculin to lie in the hyperæmia and hyperleucocytosis of the glands and their surroundings resulting finally in encapsulation, capsular thickening and closing of the vasa efferentia. He has been able regularly to prove this fibrous thickening of the capsule and the more or less complete calcification of its contents in comparative Röntgen photographs by more distinct isolation, greater



plasticity and sharper definition of the edges. Bauer and Engel [100] express their full agreement with this conception of the tuberculin cure of glandular tuberculosis as a whole; they have never seen softening of the glands, even when these were so superficial that changes must have attracted attention. Dautwiz only uses Koch's old tuberculin for strong children when it is borne without reaction; otherwise he prefers the milder Béranek tuberculin, according to Sahli's principles.

**Jochmann.**

Jochmann [171] reports as follows on the excellent results in tuberculosis of the glands in children: "Children with scrofulous taint, thickly swollen glands in the neck and scrofulous eczema, also those with swelling of the bronchial glands, shown in Röntgen photographs, flourished under tubercular treatment and gained continuously in weight. The scrofulous appearance improved, the glandular swelling diminished and disappeared. These changes were all the more striking as they were largely children who had formerly been treated with the usual symptomatic remedies without success. We used, besides old tuberculin, TR."

**Authors' Experience.**

We have ourselves often observed that the familiar picture of the row of cervical glands, like a string of beads the size of haricots or larger, disappearing without leaving any trace under treatment with Koch's preparations, or decreasing till they become hard, fibrous cords. If softening has really occurred in larger glands with central caseation, no longer capable of absorption, assistance is obtained by simple puncture or a small incision and suction. Rarely is total extirpation necessary. Wilms [127] even warns for special forethought in removing these protective organs in youth; "but when caseation and suppuration render operation necessary, then the fortification of the body against the infection, to-day both possible and appropriate, must not be neglected." Hewlett takes the same view in recommending periodical tuberculin treatment after removal of glands to attain immunity.

Krause has obtained surprising results, both in small hardened glands and also in those which had already begun to suppurate and had led to the formation of fistulæ. Schnaudigel reports similarly.

W. Neumann [277] observed under TR, BE and tuberculinum purum, tubercular lymphatic glands with and without suppuration, with and without the formation of fistulæ, heal quite smoothly even with the complication of severe pulmonary tuberculosis. The healing was often proved anatomically.



**Various Tuberculin Employed.** Reunert cured with TR a case of tonsillar tuberculosis and observed swellings of glands and spleen diminish during the treatment. In a case of tuberculosis of the iris, accompanied by a progressive tubercular infection of the lymphatic system resembling pseudo-leukæmia, the disease was arrested. Sahli uses Béraneck's tuberculin with success, Wright TR, F. Krause, M. Elsässer, Butler Harris, Turton, and Parkin bacillary emulsion, Rosenbach his own tuberculin. Klebs reports the cure of 100 per cent. of cases of tuberculosis of the lymphatic glands with tuberculocidin and selenin. Jacobs also reports complete cures with his preparations, which Lespinne confirms from his own experience.

**Use of Serum.** Marmorek's serum also has been employed with success by Wohlberg, Ullmann, van Huellen, F. A. Elsässer, and Röver in scrofula and glandular tuberculosis; they saw remarkable improvement and even cure. Preleitner's experiments in glandular tuberculosis of children were quite negative, those of Szurek unsatisfactory.

**In Tuberculosis of Bones and Joints.** Of old tuberculin in tubercular disease of bones and joints favourable report is made by Ullmann, Lüdke, Aronade, Pogue, Medowikow, Jones, Smith (thirty-four cases), Cathcart, Macleod, Loewenstein,

**Use of Old Tuberculin.** and others. At the meeting of the Research Society, in 1908, Schlossmann and Engel reported good results from old tuberculin in tubercular diseases of the bones and joints in young people, giving demonstrations with Röntgen photographs; they brought about a complete anatomical cure in two cases of spina ventosa, one case of tubercular knee-joint and one case of tuberculosis of the ulna with abscess formation and necrosis. In the larger treatise already quoted Engel completes his report on the most favourable results of tuberculin at the Dusseldorf Academic Clinic for Children in cases of tuberculosis of the bones and joints. A typical case of caries of the ribs was cured by Deterding and de Groot with twenty-three injections of tuberculin, one case by Roebroek with Denys' tuberculin. This tuberculin has also received Westerveld's recommendation for the treatment of surgical tuberculosis. Ormond cured four severe cases of tubercular periostitis with tuberculin.

**Lenzmann ;  
Intrafocal  
Treatment.**

Elsewhere, too, old tuberculin has recently been used more frequently in surgery, for instance, for tubercular ulcers and severe granulating fistulæ. Thus Lenzmann [278]



has seen the finest results in soft tubercular granulations, which had been several times removed without success and always proliferated again. According to Lenzmann, if the shedding of the tubercular tissue presents no obstacle, one can proceed with rapidly increasing doses, provided that there is no complicating tuberculosis of an internal organ, especially of the lung; should there be a complication the tuberculin treatment is regulated by it and great caution must be used. In suitable cases, especially in tuberculosis of the carpus and tarsus, he recommends intrafocal injections; the tuberculin is injected into the tubercular focus along with liquid paraffin and is used to retain the tuberculin longer in the focus. He has had very satisfactory results.

In Tilman's section of the Cologne Academy for Practical Medicine, old tuberculin is employed for all forms of surgical tuberculosis, operative treatment being limited as much as possible. Bungart [279] observed in many cases a striking increase in strength and appetite and sometimes also a favourable effect on the temperature. Present experience shows that the domain of specific treatment is in those forms of the disease in which conservative measures are considered sufficient, but also necessary operations are no contra-indication for tuberculin treatment.

**Jochmann.**

Here also Jochmann has had wide experience and expresses his opinion as follows: "In tuberculosis of the bones and joints we had in many cases a quite striking improvement in the general condition. The effect on the local trouble was varied. One case of tuberculosis of the foot healed, others of tuberculosis of the glands and joints with fistulæ, in spite of prolonged treatment, showed no change. I consider that surgical treatment takes the first place for the improvement of local symptoms in the treatment of tuberculosis of the bones and joints, but that tuberculin treatment is of the greatest importance as an aid, especially as tubercular bone trouble is not generally the only localization of the tubercular virus, but usually tubercular glands, bronchial or mesenteric, are also present, which are dangerous to the patient and therefore require to be cured."

**F. Meyer.**

Meyer [264] similarly recommends the combined surgical-specific treatment "in all cases of open bone and joint tuberculosis with fistulæ; whether an operation scar has incompletely closed with fistula formation or tubercular abscesses have broken out—complete healing can almost always be obtained by simultaneous surgical and tuberculin treatment."



**Bandelier and  
Roepke.**

**Use of TR.**

We ourselves have published reports on the action of TR in tubercular joint and bone affections [280]. Of the two classes of case, the one treated conservatively with general remedies, the other with abscess and fistula formation which had to be submitted to resection, both also treated with tuberculin, we gained the impression that the cavities remaining after the resection of the diseased ends of the joints rid themselves more easily of the tissue to be thrown off than we had formerly been in the habit of seeing.

**Brunzlow:**

**Knee-joint.**

Brunzlow also reports a case of tuberculosis of the knee-joint which, in spite of opening and cleansing of the joint and the use of iodoform-glycerine injections and Bier's congestion, visibly grew worse. After four treatments with TR, repeated at intervals of several months, a complete cure was obtained with good action of the joint.

**Powker,  
D'Arcy Power and  
W. Neumann.**

Recently Powker and D'Arcy Power have reported on the favourable action of TR in surgical tuberculosis; Sonnenburg, too, saw good results in tuberculosis of the joints. W. Neumann [277] obtained a perfect cure, even when accompanied by extensive pulmonary tuberculosis, in fungus of the joint and cold abscesses in caries of the bone. He considers TR, bacillary emulsion, and tuberculinum purum to be equal in their action.

**Rosenbach's  
Method.**

The latest modification of specific treatment is Rosenbach's method; he has used it in a large and varied selection of cases of surgical tuberculosis (joints, vertebra, tendon-sheaths, glands, fistular abscesses of subcutaneous tissue), generally with the help of various surgical methods, and has had considerable and lasting success. Wherever possible he injects the tuberculin direct into the focus; he considers the subcutaneous method only advisable in cases where direct application is impossible. The value of the treatment is confirmed by H. Curschmann, who cured a case of tubercular periostitis, also by Seyberth, who witnessed considerable improvement in eight out of ten cases of local tuberculosis.

**Marmorek's Serum.**

Marmorek's anti-tubercular serum has been increasingly used in cases of surgical tuberculosis. Favourable verdict is given by Bassano, Dubard, Lewin, v. Rotschild, Brunier, Hymans and Polak Daniels, Uhry, Sikemeier, Mühsam, Strauss, Schenker, and Weitling.



Wein was able to report a favourable effect in each of his fifty-nine cases. Sonnenburg noted a striking cure of tubercular disease of the rectum, which he had treated in vain surgically. And other favourable results were observed in the Moabite Hospital, reported on by van Huellen. Recently, however, he has become somewhat more reserved in his estimate of the serum; now prefers the subcutaneous injection, and application *per rectum*, which often produces trouble in the intestine, he regards only as a makeshift.

The judgment of Hoffa [281] is the most favourable of all, on the basis of results in forty cases of osteal and arthritic disease. He obtained improvement in cases which had defied every other form of treatment for years. In twenty-two cases under long observation he saw 18 per cent. of cures and the same striking improvement, never any harm or unpleasant secondary action after he has begun to employ the Marmorek serum *per rectum*. He recommends it, however, always in combination with other well-proved remedies and methods.

**Glaessner's Success with Marmorek's Serum.** After Glaessner [282] had seen these results in Hoffa's cases, he experimented on a large scale in the Surgical University Polyclinic. So that no mistake might be made, only out-patients were treated under quite unchanged domestic and hygienic conditions, internal medicaments as far as possible avoided, and the local disease processes, fistulæ and ulcers treated with quite inert remedies. Only in cases of tuberculosis of the joints were the most necessary surgical measures resorted to: puncture of abscesses, rest, and clearing of the joints, with Bier's congestion. Of 100 patients, seventy-two were treated for a long time *per rectum*, without any undesirable secondary symptoms arising, except temporary diarrhœa in a few cases when the injections had been administered several days in succession. From the detailed accounts of forty-eight cases, the following results are evident: Many cases of spina ventosa show no specific effect from the serum; the same is true of the cases of tuberculosis of the bones and joints in which there was a closed process, whereas in open forms, especially in fistulæ of the bone of long standing there was at least for a time a diminution, and often a rapid absorption of the secretion; one case of tuberculosis of the sheaths of tendons remained unaffected; the most striking was the diminution and in some cases the total disappearance of swollen lymphatic glands. Glaessner considers the chief advantage to be the extraordinarily favourable influence on the general condition which almost always takes place, and which would in itself alone justify the use of the



serum. Altogether he considers Marmorek serum in conjunction with other proved methods of treatment as a valuable weapon in the campaign against surgical tuberculosis.

**Unfavourable  
Reports.**

On the other hand, Hohmeier's reports are very reserved; he could not see signs of a definite curative influence of the serum even in slight, fresh disease of the bones and joints; in cases of average severity, and in severe cases it was completely ineffectual. Preleitner also saw no results in tuberculosis of the joints in children. Sonntag also says that the curative action of the serum is difficult to estimate.

**Lenzmann's  
Conclusions as to  
Use of Serum.**

Lenzmann [278] draws the following conclusions from the above surgical publications. A precise surgical indication for the application of the serum must not be neglected. It should be employed when conservative treatment is permissible on other grounds, and when it is a question of hastening the result of an operation and of ensuring its success. In all such cases the critical estimation of a real cure is rendered very difficult, as it often involves prolonged periods of treatment, in the course of which many a surprising change for the better may occur. Still the favourable reports are so numerous that specific antitoxic powers cannot be denied to the serum. Harmful results have not been noticed in surgical tuberculosis. The method of application *per rectum* is uncertain. Further study of the effectiveness of the remedy is desirable.

## 10.—TUBERCULOSIS IN CHILDHOOD.

All that has been said of tuberculin treatment for the adult applies also to children, but even greater care is indicated.

**History.**

After Ganghofner in 1905 and a year later Jessler, declared themselves disciples of tuberculin treatment, and tested it in cases of infantile tuberculosis, the question was more closely considered, but tuberculosis of the glands and surgical tuberculosis remained the principal subject of therapeutic inquiry. In 1907 Engel [283] in an excellent treatise on the reasons for believing in the curability of pulmonary tuberculosis in children, only thought it advisable that experiments should be made with tuberculin, on the result of which was to depend whether "a definite specific treatment of tuberculosis in children should be inaugurated or whether all such experiments were to cease." In the meantime tuberculin had already found its way into some children's hospitals and the



experiences collected from such hospitals (for example those of von Landgraff and W. Goetsch) were favourable. Also, according to the information given by K. Pannwitz the results at the Hohenlychen Red Cross Children's Hospitals were considerably improved by the assistance of tuberculin treatment; the children increased on an average more in weight and lost the tubercle bacilli in 46.5 per cent. of cases, as against 25 per cent. when the hygienic-dietetic treatment was used alone. But especially the recent work of Schlossmann and his assistants, Bauer and Engel, has opened up more hopeful prospects as regards pulmonary tuberculosis in children.

**Tuberculin  
Treatment of  
Sucklings.**

Although according to recent investigations, especially those of Hohlfeld, there is in the lungs of sucklings who have died of tuberculosis an occasional tendency to heal, yet the prognosis of tuberculosis in sucklings is a very unfavourable one (Weigert, Schlossmann, Naegeli, Stirnimann and Geipel, Hamburger and Sluka, Engel, and others). The fact is therefore important that Schlossmann [284] has succeeded by systematic treatment with tuberculin in bringing sucklings safely and in good condition through the most dangerous year, the first year of life; whereas other sucklings, not treated specifically, but cared for in other respects like the former, died.

**Dosage  
for Children.**

Hitherto, in treating tuberculosis in children, very much smaller doses have been used than with adults, and a beginning has been made in small children with one-tenth, with bigger ones with  $\frac{1}{4}$  to  $\frac{1}{2}$  of the dose prescribed for adults. The maximal dose, too, has remained correspondingly lower than that for adults. Schlossmann also begins with small doses (0.01 to 0.1 c.mm. of old tuberculin) and especially at the beginning of the cure uses the mild form of treatment in a cautious manner, carefully adapted to the individual, but without entire avoidance of slight or moderate reactions; he seeks, however, to reach exceptionally high doses, greatly exceeding those given hitherto (2,000, sometimes even 5,000 c.mm. of old tuberculin). But he points out emphatically that this method applies only to children in the first year of life. He thus maintains the principle we have upheld for years, that tuberculin treatment should begin with small doses leading up to large doses, a principle which, however, so often appears to be misunderstood and has no connection with and is by no means identical with the production of severe reactions. Schlossmann finds support for the expediency and necessity of large doses of tuberculin in the interesting investigations of his assistants



Engel and Bauer (*cf.* above), who with the help of fixation of complement were able to prove that the tubercular children treated with tuberculin showed in their serum a formation of antibodies in proportion to the size of the tuberculin dose. But the proof of the presence of such antibodies was only obtained in the children when inoculated with 100 c.mm. of old tuberculin and upwards. So the aim of tuberculin treatment must be to enable the child's body, by doses systematically increased, according to the individual susceptibility, to tolerate the quantities necessary for an active formation of antibodies. And the formation of antibodies must be maintained by the prolonged injection of the larger doses—about 500 to 2,000 c.mm. every five to eight days. Schlossmann describes tuberculin as the best therapeutic aid in the campaign against tuberculosis in children.

**Engel and Bauer's** In a very detailed work [100] Engel and  
**Conclusions.** Bauer published the results of their studies of the pathology and treatment of children's tuberculosis, which contain the clinical and experimental proofs of the above conclusions of Schlossmann. The special result of these investigations can be summarized in the following statements, which we emphasize on account of the fresh guidance they afford for tuberculin treatment.

All tubercular children who are free from pulmonary tuberculosis are, without exception, suited for tuberculin treatment, so that there are scarcely any contra-indications.

The latent form of tuberculosis, only manifested by the positive tuberculin reaction and scrofula, must—from the point of view of formation of antibodies—be considered as specially favourable for specific treatment.

Fresh cases of pulmonary tuberculosis, above all progressive cases, are not suitable for treatment with tuberculin.

Lung processes of small extent with but little tendency to increase are amenable to cautious treatment with tuberculin.

The younger the children, the smaller appears the prospect of cure.

A low state of nutrition is to be considered rather as an indication than as an contra-indication.

Fever is not an absolute contra-indication; in many cases fever can be got rid of by small doses of tuberculin.

The investigations of Engel and Bauer would seem to have proved that the child's organism—independent of age—is not so susceptible to tuberculin in cases of localized tuberculosis as was hitherto supposed; that the degree of susceptibility to tuberculin is not only dependent upon the extent of the tubercular process,



but also on its activity and tendency to increase, *i.e.*, on the prognosis.

**Indications and Contra-indications.** So cases of localized tuberculosis of glands, bones and joints with favourable prognosis are little susceptible to tuberculin and easily rendered immune to it. Pulmonary tuberculosis tending to increase and of unfavourable prognosis is extremely susceptible to tuberculin and scarcely open to systematic treatment. They are borne out in this conception by Heubner, Soltmann, Escherich and others, who also failed to attain satisfactory results with the smallest doses of tuberculin, and preferred to abstain from using tuberculin altogether in cases of pulmonary tuberculosis in children. Slighter cases of pulmonary tuberculosis tending to become stationary, and mostly situated in the upper portions of the lung, form intermediate cases.

Jochmann obtained good results in cases of pulmonary tuberculosis in children over 3 years of age. But here also it was only a question of slight cases of apical disease, with but little dulness and thickening in the Röntgen picture. Tuberculin treatment of pulmonary tuberculosis in sucklings was unsuccessful.

**No Fundamental Difference between Tuberculin Treatment of Adults and Children.** From the works of Schlossmann, Engel and Bauer, we see not only that the different susceptibility to tuberculin of the child organism is explained by one uniform fundamental law, but to our surprise we also learn from these extensive publications that the mode of reaction to tuberculin is in the main the same in cases of tuberculosis in adults and in children. And so we can no longer acknowledge any fundamental difference in the therapeutic use of tuberculin in adults and in children in contradistinction to Engel and Bauer, who still maintain a difference owing to lack of personal experience in tuberculin treatment. Moreover, their method of treating pulmonary tuberculosis is almost absolutely identical with our proposals for the treatment of adults with old tuberculin, both as regards the initial doses, graduation of dose, the best maximum dose, the interval, the length of treatment, and the general principle underlying the treatment.

We may pick out two important points from these careful and very thorough investigations which show the progress made:—

(1) An important contribution to the fixed laws of the action of tuberculin on the tubercular organism.

(2) Fresh support given to the utility of modern tuberculin treatment as we advocate it, from the clinical and biological point of view.



**Unsuitability  
of the Method of  
Large Doses.**

The method of large doses of tuberculin for children has not found very general recognition. Toeplitz recommends it with slight modifications for ambulant treatment. Baginsky, Citron, Cohn, Escherich, Ganghofner, Hamburger and Monti, Jochmann, Weddy-Poenicke, and Wolff-Eisner have expressed themselves adversely. J. Neumann reports the observation of complete change of temperature and subnormal depressions. Fuchs in thirteen cases of surgical tuberculosis and five cases of tuberculosis of the apices did not observe a single success, but often even a bad result. Rohmer [285], too, could not prove this treatment to be frequently successful, although clinically a striking curative effect was found with regard to scrofulous symptoms and anatomically an abnormally strong proliferation of connective tissue, especially in the region of pulmonary foci, to which phenomena Dautwiz has repeatedly drawn attention. When continuous use of large doses was made, in most cases hypersusceptibility set in, and it seemed as if large doses of tuberculin had a prejudicial effect on the general well-being of the children. Also, in spite of prolonged treatment, the extension of the tubercular process did not always cease. Rohmer, therefore, advises a return to the moderate doses formerly used.

**Treatment  
by Small Doses,  
Gradually Increased  
Preferable.**

The treatment of tuberculosis in children commencing with very small doses gradually increased receives increasing recognition. Thus experts such as Escherich and v. Pirquet consider the method extremely valuable as long as there is no manifest tuberculosis but only lymphatism, pallor, and weakness, with positive cutaneous reaction; for such cases, ambulant tuberculin treatment is also thoroughly suitable. Cronquist and Wittich have also just published very favourable results in a suitable selection of cases. The latter, issuing his report from the Royal University Clinic in Berlin, gives an equally warm recommendation of the ambulant tuberculin treatment of children suffering from scrofula, incipient tuberculosis and tuberculosis of the bronchial glands. The results can be summarized thus: Cough, pain in the chest and stitch disappear; night-sweats cease; diarrhoea gives place to a normal stool; the appetite, weight, and general condition improve; scrofulous signs, phlyctens, and tuberculides of the skin vanish.

**When should  
Tuberculin Treat-  
ment Commence?**

When should the tuberculin injections be commenced in childhood?

v. Leube [286] expresses our own opinion in the following quotation: "As



we may assume that tuberculin treatment increases the specific resistance of the organism to the toxins of the tubercle bacillus and counteracts their harmful effects, the cure should be begun as early as possible in order that the transition from the closed form of tuberculosis to the open form may be prevented. The best method of procedure is, in the case of

**Value of** children of tubercular parents, to make  
**Cutaneous Test.** repeated v. Pirquet tests so as to determine the time of the first infection with tubercle bacilli. Such diagnostic tuberculin tests repeated at fixed intervals by the family physician or dispensary doctor belong to the regular medical family supervision, the necessity of which is justly receiving increased recognition. As soon as a positive v. Pirquet reaction is observed, tuberculin treatment should be commenced. The cure must last several months, and should be repeated later; it can be carried out by the physician at home or in a dispensary, in the health resort or sanatorium."

Lastly, v. Leube's injunction is in agreement with the old demand of Koch—to discover all early forms of tuberculosis by the aid of tuberculin diagnosis and to cure them with tuberculin before they reach the stage of open tuberculosis. Since 1897 Petruschky has been especially enthusiastic in his unremitting recommendation of this method of combating the disease. After the discovery of v. Pirquet's test, A. Krause [287] again brought it into recognition by advising the systematic performance of the cutaneous test on all children from 2 years of age upwards, and curing those that react by tuberculin treatment before they reach the school-going age. In the last place, Citron [288] at the International Tuberculosis Congress at Rome in 1912 has developed the same idea and demands a systematic fight against the disease in childhood. On the ground of all our biological knowledge and our clinical and experimental experiences in tuberculin therapy we may assume that the resistance of the organism infected by the tubercle bacillus is so raised by tuberculin, especially bacillary emulsion, that manifest tuberculosis does not develop. He emphasizes the fact that this method must be adopted on the larger scale "if a serious attempt is to be made to solve the great and difficult problem of the fight against manifest tuberculosis."



## Conclusion.

---

### Value of Specific Treatment Established.

THERE lies before us a record of numberless successful results in the different departments of tubercular disease, results obtained with all kinds of products and substances from the tubercle bacillus by active immunization and with serum. Passive immunization seems to prove useful only in a certain percentage of cases of initial and purely local (especially surgical) tuberculosis. In spite of the success thus obtained, the future of the specific treatment lies in the direction of active immunization, tuberculosis possessing all the characteristics of a chronic disease. The results hitherto attained confirm this view. Perhaps further progress may lead to a combination of active and passive immunization. At any rate, in face of the great mass of accumulated facts, belief in the value of specific treatment cannot be any longer withheld. Future research may perhaps succeed in finding a better remedy, a universal panacea for the disease; we hope and desire it. But the present generation cannot spare the time to wait for this; practitioners and patients alike are thrown back on the remedies now available. And of these remedies the value of the tuberculins is too little known and appreciated, first and foremost among them being the preparations of Koch as the most tried and approved.\* To help to assure them the position they deserve in extending the healing art and adding to the comfort of the suffering whom we all serve, has been the sole object of this book.

### Opponents of Tuberculin.

A few words of defence, as were necessary in former editions, are no longer needed to-day. The time when a certain number

\* It should be noted here that in Germany tuberculin is subjected to a Government test, without which it may not be sold. This test is an absolute necessity in view of the large number of preparations which home and foreign industry has put on the market. It is the only guarantee for uniformity of preparation and will, it is hoped, lead to reduction of preparations in use to some of the best proven. We emphasize the importance of this Government test, as there is no reference to it on the tuberculin bottles nor on the accompanying circulars.



of our colleagues lost no opportunity of emphasizing their dissent with more or less skill, dignity and urbanity, is over. There is no longer an open feud against tuberculin. Tuberculin is recognized as the one highly specific remedy in tuberculosis, and the general feeling is expressed by the words of F. Klemperer [289]: "I have no right to say that tuberculin is not an effective remedy"; or some go so far as to say with him that they consider "tuberculin a good auxiliary in the treatment of tuberculosis." Each is entitled to his own opinion, and we only claim the right to oppose error, timid doubt, and blind faith where their fruits counteract progress urgently demanded by the state of affairs. But we cannot pass over the voices and ignorant statements of recent anti-tuberculin literature without a word of disapproval. Whilst more or less reservedly recognizing the value of tuberculin, they object to the extent of its employment; this extended use seems to us not only possible, but, in the interests of a successful fight against tuberculosis, absolutely necessary. Tuberculin is no longer openly and definitely rejected as this would be too committal, but doubts and objections are raised which, although without any real justification, are able to do harm. For the practitioner is more attentive to the cry of warning than to the warmest expression of approval, and prefers to wait rather than to act, as he supposes, prematurely. It is to these tactics, which are intended to retard the victorious work of specific diagnosis and therapy, that we object.

#### Diagnosis.

In the interests of truth and accuracy, we will first turn to the question of tuberculin diagnosis. Schroeder [290], in his recent work, "Tuberculin Treatment," summarizes the section on tuberculin diagnosis as follows: "The chief result of the debate" (at the yearly Congress of Sanatorium Doctors, at Düsseldorf, in 1911) "was the rejection of tuberculin as a diagnostic agent for the recognition of *active* tuberculosis in adults." What was really said at this Congress? Meissen [291], who, in his lecture, "Experiences with Tuberculin," expressly denies that he has been converted from a Saul to a St. Paul in the question of tuberculin, says that he considers the value of tuberculin lies more in its use as a diagnostic agent than as a therapeutic remedy. Ulrici [112] opened the discussion on the "Question of Tuberculin for Ambulant Practice" and in speaking of the diagnostic use of tuberculin gave his opinion that no help in practical diagnosis of adults is to be gained from the *local* tuberculin tests and that the subcutaneous test should be excluded from *ambulant* practice. In the discussion which followed Junker disagreed and stated



that tuberculin diagnosis, used with observance of the various early symptoms of the disease, is a valuable adjuvant, but should only be employed by doctors possessing considerable experience. Koch observed focal reactions after test injections a good deal oftener than Ulrici, and they never caused any harm; he had also never been able to convince himself of the danger of the conjunctival test performed on the healthy eye. Krause, on the contrary, had but seldom recognized definite focal reactions, and has often seen conditions which can be described as harmful, and which lasted for some time. Curschmann considers the diagnostic tuberculin test used for the diagnosis of pulmonary patients for sanatorium treatment worthless. Brecke took precisely the opposite view; he held that Koch's test together with other methods of examination will always remain a most valuable adjuvant in diagnosis, and is absolutely indispensable if as many tubercular subjects are to be diagnosed in the initial stage as possible, as is demanded by the very principle of the campaign against tuberculosis and the scheme of National Insurance. Ulrici then explained that he only rejected the *local* tuberculin tests, and the subcutaneous in ambulant practice. But even if his opinion be counted as unconditionally opposed to the value of tuberculin diagnosis. Schroeder's statement is an absolute misrepresentation of the facts, quite different and opposed to what was really said; there were at the Düsseldorf Congress at least as many voices raised for tuberculin as a diagnostic agent as against it. Therefore it is deplorable that Schroeder, who has certainly had no very wide experience in this branch, sets his own judgment over other and more competent authorities, misrepresenting them, even partly reversing their real views and in one sentence misleading the less read medical world. Although personal polemics are very distasteful to us, we desire to see this matter righted, in order that Schroeder's criticism of tuberculin diagnosis shall at any rate not find its way from medical to public literature without refutation. As a rule the very fact that it was a bequest from Robert Koch will itself protect the specific diagnosis of tuberculosis from rejection. Let us realize the ten years' fruitless effort to find a specific reaction for syphilis, which has given us the Wassermann test, but which is even now not always and for all cases absolutely certain. Or we can compare the still unsatisfied desire for a specific reaction for carcinoma. Then we shall fully realize the fundamental significance of the epoch-making and practical tuberculin diagnosis. It will not be disposed of by a single sentence or a single discussion, not even limited by a few records of so-called tuberculin damage. What do we learn from Penzoldt and F. Kraus, two university



professors certainly not prejudiced in favour of specific diagnosis? Penzoldt [105] states that the disadvantages of the subcutaneous test are negligible; and Kraus [258] but a short time ago in a post-graduate lecture for practitioners made the following statement with reference to pulmonary tuberculosis: "Every injection of tuberculin brings about quite a characteristic condition in the tubercular. According to the severity of the reaction, muscular pains, languor, increased pulse-rate, nausea, fever and headache occur. With these, after twenty-four to thirty-six hours, the signs of a local reaction appear—increased sputum, catarrhal sounds, stitch on the diseased side, sputum containing bacilli and changes in the physical signs. As all these symptoms soon disappear and give place to an increased feeling of well-being, we have no ground for any special fear of them. How favourable an effect an injection may have can be easily seen in ulceration of the larynx which is visible to the eye, in which distinct anatomical changes are seen after each injection, first in the direction of aggravation of the condition, then of a healing process. Similarly it is possible to demonstrate the anatomical effect on tubercular changes in the lung."

**Treatment:  
on the Ground  
of Resulting  
Harm;**

We now come to the therapeutic use of tuberculin. It is true that harm *has* resulted from the use of tuberculin, but this was in a previous epoch, the early stage of development, a time in which the first attempts were made on unsuitable material and based also on a false view of the action of the remedy, heedless of the warnings and cautions of Robert Koch. The few more recent unfavourable reports are all to be referred to faulty application or unsuitable selection of cases.

Moreover, it is a fact that the unfavourable or less satisfactory results are recorded by observers who have had but little experience of the method, and that they receive no confirmation from clinicians who have for years worked with the remedy. It may be asserted that not a single case has been published in which the alleged harm has resulted from the mild, reactionless method of administration recommended by us. All this should make one wonder whether the harm has not been a consequence of a faulty method, and whether it could not have been avoided with certainty by carefully following the directions, indications and contra-indications. And the conviction is brought yet nearer home when we see men of scientific attainment formerly opponents of tuberculin become advocates of it after working for years with the modern mild method of administration and assuring themselves not merely of its safety but of its superiority to other treatment.



And the number of these specialists and clinicians has lately enormously increased with the increased use of tuberculin preparations—a numerical and living proof that there is no danger of harm from the use of tuberculin with the modern system of injection.

**on the Ground  
of Animal  
Experiment.**

In the second place, its opponents adduce the fact that tuberculin generally fails to cure the artificial infection of guinea-pigs and rabbits. Here it must be admitted that the cure of infected animals by means of tuberculin preparations has only been attended with success in the hands of the few workers who have specially taken up this laborious investigation: for example, R. Koch, Kitasato, Bujwid, C. Spengler, Pfuhl, Dönitz, Klebs, Yamagiva, Sattler, Centanni, Landmann, Christian, and Rosenblat. Other observers (such as Baumgarten, Alexander, Gasparini, Mercanti, Baas, Popoff, Liebmann, Metchnikoff, Roux, Buchner, Laffert, and recently Stumpff and Haupt [292]) observed neither inhibition nor healing of tuberculosis in experimental animals. The positive observations are, however, not to be denied, and are not rendered less credible by the experiments of Krusius [293], who, in artificial intra-corneal tuberculosis of rabbits, recognizes a relative protection afforded by prophylactic tuberculin injections, but no real healing action of therapeutic injections. It is true, too, that Titze did not succeed in curing tubercular guinea-pigs by tuberculin, but showed that the tissue-reactions caused by the tuberculin treatment are the commencement of the healing processes which result in encapsulation of the tubercle bacilli in the tissues. The usual

**Unsuitability of  
Animals Used.**

small animals such as guinea-pigs and rabbits are certainly very unsuitable experimental subjects. The artificially infected guinea-pig invariably dies of general tuberculosis after injection of the smallest quantity of living tubercular material even in a dilution of 1:1,000,000,000.

**Other Reasons for  
Non-success.**

There are, too, a large number of further reasons why a therapeutic attempt with tuberculin in animals does not run parallel with the tuberculin treatment of man. Kraemer [294] has stated amongst others the following: The conditions of healing are altogether unlike in man and animals; the absolutely different behaviour of the organism to certain infections and toxins is a matter of common knowledge; there is a fundamental difference in the manner of the natural and of artificial infection in animal experiment; artificial infection in the small body of the experimental animal is always much too severe.



**Necessity for  
Long Treatment.**

Further, immunizing experiments in animals show that immunity to tuberculosis is less complete and less stable than immunity to other infectious diseases. This will hold, too, for man. Therefore we advise a prolonged course of tuberculin treatment (by the family doctor, &c.), so as to maintain tox-immunity and production of antibodies and to avoid relapse. As Schroeder states that he has specially often observed relapses in highly immunized tubercular individuals, we must state precisely the opposite—that amongst many hundreds of highly immunized patients kept for a long time under observation, we have not made such observations.

**Views of  
v. Behring and  
Neufeld.**

It must lastly be borne in mind that v. Behring, in his studies of tubercular immunity, gave up experimenting with rabbits and guinea-pigs on account of its great difficulty. "The task of rendering a guinea-pig tuberculo-immune," v. Behring says, "is actually more difficult than that of immunizing cattle, and this is principally due to the fact that the sequence and dosage of the agents cannot be determined without accurate registration of temperature and body-weight, of the local and general tissue changes, of the alterations of the blood, &c." Hence we have a right to demand at any rate experiment on larger animals, of which cattle are specially suitable. Neufeld also [295], long a co-worker of Koch's, is of the opinion that the bovine infection of cattle, well known to be of milder course and with tendency towards spontaneous cure, has a far closer analogy to human tuberculosis. And in fact v. Behring has recorded the excellent healing action of old tuberculin on tubercular cattle. McFadyean and Pearson and Gilliland, too, have succeeded in producing a high degree of immunity with tuberculin in cattle suffering from bovine infection and artificially infected.

**Necessity of  
Combination with  
General Treatment.**

The second edition of our handbook, "A Clinical System of Tuberculosis" (Bale and Danielsson, 1912) makes it quite clear that we agree with the general hygienic-dietetic treatment of tubercular patients. We consider the combination of the two modern factors—sanatorium and tuberculin treatment—the most efficacious method of treatment for active pulmonary tuberculosis at present available, especially when the disease has passed the initial stage. We are emphasizing here the combination with non-specific treatment because the value of sanatorium treatment seems to lie in two directions: (1) It affords the exclusion of all harmful factors of the workers' daily life, of the home,



of the persistent exposure to infection, and of an unhygienic mode of life in the fullest sense, factors which have so extraordinarily powerful an influence in so many chronic diseases. (2) The general treatment—physical, dietetic and hydriatic—is intended to strengthen the resistance of the organism, to increase its total vital energy, and to stimulate the depressed and weak by rest or methodical exercise. We advocate this standpoint without the value of general hygienic-dietetic treatment of tubercular patients having been proved by experiments on animals. But we ask the opponents of tuberculin, who to-day only call themselves sceptics, what would be left of the whole armoury of our treatment of phthisis if the same demand were made of the generally recognized curative factors, especially of the hygienic-dietetic *régime*—that they should cure experimental animals. No such proof is needed by the physician who has worked for any length of time "*lege artis*" with tuberculin. More convincing than experiments on animals is one's own personal accurate observation and experience at the bedside, to which Sahli rightly alone admits authority in the tuberculin question, as in all questions of therapy.

**Co-operation of  
Medical  
Fraternity.**

When, after a standstill in the rate of mortality from tuberculosis, the numbers again decreased and sank to the lowest point hitherto reached, it seemed as if our great organization against tuberculosis had reached the limits of its powers; but it has now been strengthened and advanced by the more extensive use of specific therapy. Once more we must strive to the goal which we have had in view for years: the co-operation of all medical men, especially general practitioners, in the treatment of tuberculosis and with specific remedies. Experiences have been so completely sifted and the results so thoroughly tested that tuberculin by the new method can be recommended to a much larger circle of physicians for their own use.

**Reasons for  
Large Number of  
Tuberculins.**

We now possess a definite well-based tuberculin therapy, that of the mild, gentle form of administration. This fact is not altered by the comparatively large number of preparations recommended and the variety in the methods of administration proposed, which is complained of by F. Klemperer [289] and others, and which has been interpreted as a sign of the failure of tuberculin treatment. This is not so. Tuberculin is no universal cure for tuberculosis; the limits of its power are sufficiently known. What is more natural than by continued reasearch and freshly acquired knowledge to seek more effective immunizing substances? The fate of other remedies such as iron



and iodine is exactly similar; what a vast number of preparations, but who would doubt the value of the substance common to them all? This is scientific progress; a standstill means retrogression. Just as in treatment with iron, salicylates, mercury and iodine, so in tuberculin treatment the result depends less on the choice of the preparation than on its correct employment. Moreover, there

**Only Two  
Different Kinds of  
Tuberculin.**

are really only two essentially different kinds of tuberculin—old tuberculin preparations and bacillary preparations; all others are unimportant modifications. The mildest representative of the first group is albumose-free tuberculin (AF), with which the practitioner can work most successfully. If it is necessary to employ a bacillary preparation, we can recommend as the mildest of all the sensitized bacillary emulsion (SBE); further details have been given in the separate chapters on the tuberculins.

**Tuberculin the  
Concern of the  
General Practitioner.**

We consider it, therefore, the problem of the present day to introduce tuberculin treatment into general medical practice. The recognition of its efficacy makes this not only our right, but duty. It is true that those practitioners who have only just given up the fight against tuberculin, and also some who know and value the curative power of tuberculin, are not yet quite of this opinion. But the majority of German medical men greet the efforts to lift them out of their passivity with regard to the treatment of this national disease and to equip them for successful personal treatment of their tubercular patients with great interest and understanding of the importance and difficulty of the task. The further development of the tuberculin question will not take place without work and without struggle. We fear neither and will continue to strive for the introduction of tuberculin treatment into general practice, an event both necessary and possible. But one, perhaps rather personal, remark we should like to make: the man who considers or has considered tubercle bacilli as harmless saprophytes will find it very difficult to understand the use of tuberculin; and these less old-fashioned physicians who, till a short time ago, rejected tuberculin in every form, should be the very last to set local limits to tuberculin treatment, which they now recognize as useful, limits which should cripple us in the campaign against tuberculosis as a national disease.

**Ambulant  
Treatment;**

As regards ambulant tuberculin treatment, we must distinguish between two different kinds: (1) a continuation and completion



of a course of tuberculin treatment begun in an institution, but interrupted prematurely, or (2) a course begun and carried on outside the institution by a practitioner according to his own judgment.

**After Sanatorium  
Treatment.**

In the first case we are considering subsequent treatment as an out-patient after sanatorium treatment. For the consideration of this question it is necessary to study the kind of patient and length of treatment in the public sanatoria and private institutions.

**Public Sanatorium  
Treatment too  
Short for Complete  
Cure.**

Patients who go to sanatoria consist (according to the Turban-Gerhardt division into stadia) on an average of one-third so-called initial cases, about two-thirds being patients in the second and third stadia of pulmonary tuberculosis; yet the average period of treatment in the public sanatoria is only ten to thirteen weeks. This period is not long enough to cure or to bring to a standstill, with cessation of sputum or of the bacilli in the sputum, tuberculosis spread over two or more lobes of the lung, generally not even when the sanatorium treatment is combined with the use of tuberculin. The latter must be used in carefully graduated doses and, if possible, without producing reaction, so that on an average only twenty to twenty-four tuberculin injections are possible in the sanatorium. This generally succeeds in removing all general toxic symptoms and incites the production of antibodies, which assist the curative processes at the site of disease. But hardly ever with so short a course of treatment is that high degree of tox-immunity reached which is accompanied by a continuous ample supply of antibodies, promoting the diminution and clearing of the tubercular process, the disappearance of râles, sputum and bacilli and offering some guarantee against relapse. To accomplish this, much larger doses of tuberculin, continued for a much longer time, are necessary. The result of the shortness of the combined sanatorium and tuberculin treatment is that in the more advanced cases the source of infection is not dried up, the good general condition arrived at disappears again more or less quickly, the tubercular focus with its toxic influences gets the upper hand and leads gradually to the patient becoming worse, a process which it is often impossible to arrest, even by a second course of treatment in the sanatorium.

So the doctors of the institutions are really, as Weicker expressed it, "working on a torso." "The patient generally comes to us with well-pronounced disease; the length of the stay



depends upon his economic conditions; he often leaves us at a time when a clinical cure is impossible. What happens? We discharge him with good advice, advice which in the struggle for existence he is generally not in a position to follow. A temporary improvement, a postponement of death has been achieved, but not a cure; therefore the practitioner must be asked to continue at home what the institution has begun." And this means nothing less than preventing patients capable of being cured from passing, after discharge from the sanatorium, into a condition which cannot be cured.

Now the proposal might be made that such cases should be kept longer, until clinically healed, in the institution. This would certainly be the surest way. What can be done by combined cures of a sufficient duration we have recently shown [149]: In the treatment of 500 patients in open tuberculosis of Turban's Stadium I, it was successful in 100 per cent. of the cases, in Stadium II in 87 per cent., and in Stadium III in 44 per cent. in attaining lasting disappearance of sputum or of tubercle bacilli in the sputum. But the question of expense is generally an obstacle both for private and public sanatorium patients.

The very liberal grant received to-day in the insurance scheme [in Germany] will probably be continued on the same scale, although the expenditure for the treatment of tuberculosis has during the last few years amounted to double the sum estimated. At any rate, we cannot reckon upon the length of the treatment in sanatoria being extended in the future, and clinical cure in cases past the initial stage will remain infrequent. Treatment will therefore in many cases only be able to lay the foundation on which the practitioner will have to build, in order to cure the cases of tuberculosis which leave the sanatoria not cured but capable of being cured. And for this purpose no remedy is anything like so efficacious as tuberculin.

**Private Sana-  
torium  
Treatment.**

The conditions in private sanatoria are just the same. The course of treatment is certainly often longer, but the cases, the selection of which is not subjected to any legal restrictions, are much worse. So it is a matter of daily observation that paying patients, in spite of longer treatment, do not, as a rule, remain long enough. In the large majority of cases this is due to expense. Those who are aware of the conditions know that the cost of a cure lasting many months is not covered by the income of men of the middle classes or of officers and the higher public officials, and a premature cessation of the cure is necessary unless they have private means. It is



also very doubtful policy to spend the last penny of one's savings on treatment in the sanatorium, because after discharge the conditions of life and nourishment should be as good as possible, and so extra expenditure is necessary. At any rate, in all cases when the treatment is prematurely interrupted, that is before clinical cure has been accomplished—and this, according to our experience, is the general rule—the private doctor will have to continue the treatment with injections of tuberculin if really permanent results are to be arrived at, the doctor of the institution having been forced to leave the cure unfinished owing to the pressure of external circumstances.

**Unfounded  
Objections to  
Ambulant Treat-  
ment.**

The practical possibility of ambulant tuberculin treatment is estimated differently, according to the point of view of the individual critic. Sceptics see difficulties everywhere, often where none exists; they generalize upon or exaggerate certain inconveniences until they become unsurmountable obstacles, and this in the twentieth century, when social conditions are of the greatest interest and when millions are being spent in the campaign against tuberculosis! Many an over-anxious adherent of tuberculin would like to prevent it from again being brought into discredit by uncontrolled and reckless use in general practice. Such anxiety shows the highest recognition of the value of tuberculin. But in this respect we certainly do not need to be more cautious than Koch himself, who, after his first experience, would certainly not have risked the reputation of his preparations of tuberculin in handing them over to general practitioners. Koch evidently was no longer afraid of this when he wrote in the introduction to the third edition of this text-book: "I also agree in recommending specific treatment for out-patients, naturally with the most careful selection of cases." In these words Koch approves of our standpoint, that with the modern use of tuberculin certain precautions are sufficient to guarantee on the one hand the success of ambulant treatment, on the other hand to exclude the possibility of evil results.

**Sanatorium  
Patients specially  
suited for  
Subsequent Tuber-  
culin Treatment.**

The precautionary measures demanded for clinical treatment hold good too in the subsequent treatment of out-patients. In this case only such patients are treated as have already been treated specifically in the institution, have overcome the first and greatest difficulties, and after the course of tuberculin treatment have been considered suitable by the doctors of the institution for



continued treatment as out-patients. Thus any mistake in the choice of patient is excluded. A selection can also be made so that only serious, steady, conscientious patients are suggested for subsequent ambulant treatment and the nature of their calling and the distance from the doctor taken into consideration.

Such patients also have the necessary experience in the regular taking of the temperature, the proper behaviour after injection, the observation of their own symptoms, ascertaining the body-weight, &c., and so make individual treatment and judgment easier for the doctor. Finally the doctors of the institution, who by long observation are intimately acquainted with the details of the case, can give the general practitioner certain directions for the continuance of the treatment.

If it is added that this specific after-treatment of out-patients should be purely optional, that it should not be forced upon either the patient or his private or club doctor, then everything has been said to ensure its success.

**Ambulant  
Treatment without  
Previous Sana-  
torium Treatment.**

The option of ambulant tuberculin treatment without the previous combined sanatorium and tuberculin treatment is important. We do not want to be misunderstood. We do not in any way want to underestimate the work and importance of the hospital and sanatorium; they are absolutely necessary and will remain so; and the present plan of providing sanatoria for the middle classes can only be greeted with great satisfaction. But the radius of their work is not sufficient in the campaign against tuberculosis as a national disease, even when, after introduction of National Insurance and the insurance of private employes, more than one-third of the population are included. What is to happen to the non-insured when they fall victims to tuberculosis? And even if it were possible financially and economically to place all cases of tuberculosis without delay in the sanatoriums for treatment, there would not be room for them. All the 164 sanatoria, with their 15,863 beds for adults and children and an average of three months' treatment, can take in all something like 63,500 phthisical patients yearly, leaving about half a million patients to the general practitioners for ambulant treatment. In view of these figures a certain feeling of helplessness is natural. Little is achieved by good medical advice as to rest, nutrition or water-treatment, for, as a rule, the patient in the course of his everyday life is unable to carry out this advice in such a way as to effect a cure. Very slight is the therapeutic effect of preparations of creosote and guaiacum or of the modern



and latest preparations, the curative value of which is usually doubtful or stands in no proportion to the price. The only remedy specific in its action is tuberculin, so that practitioners will have to decide to use it as long as no more effectual remedy is available for ambulant treatment. In such a situation, no debate can alter matters nor any conclusions such as that arrived at in the Düsseldorf Congress of Sanatorium Doctors (September, 1911), according to which a profitable tuberculin cure in private practice may be recognized as possible, but that there is no reason to desire or promote its wider employment. The admission of possibility has been more than justified by the facts, and the second part of the sentence over-estimates the powers of the sanatoria in the fight against tuberculosis and completely fails to realize what is really necessary—the active therapeutic coalition of all practitioners. As sanatorium physicians we feel compelled to hope that for phthisical patients who are suitable for specific treatment but who for any reason are excluded from sanatorium treatment, a successful ambulant tuberculin cure may be allotted. Therefore we also hold it our duty so to help our colleagues in private practice that they may learn to employ the specific treatment of tuberculosis according to the individuality of the particular case and with the greatest possible certainty. Thus we hope by therapy and prophylaxis to extend the fight against tuberculosis to the widest circles of our nation, and not only to combat the chronic ill-health and danger of infection of thousands, but also to counteract a thriving swindle in various bogus methods of treatment and quack remedies.

**Objections on the  
Ground of  
Interference with  
Work.**

Then it is objected that the use of tuberculin on out-patients and the necessity involved of taking the temperature periodically makes the exercise of a man's calling impossible. This may sometimes be the case but quite exceptionally, as according to the industrial regulations there is in all industries a maximum day's work, broken by periods of rest. But there is nothing to prevent the doctor from certifying the patient as unfit for work at the commencement of the tuberculin treatment, which then entitles him to the receipt of sick-pay, wages, &c. In the case of patients who are still or again fit for work, Saturday is the best time for the injection of the large doses which are less frequently needed, as they get Sunday for rest. Everything depends on the agreement and willingness of the patient and the doctor to use tuberculin treatment. That the independent middle class, those whose work is mental, housewives and members of the family, who have no



calling cannot spare time for the treatment, cannot be seriously maintained. For staying in bed or special care is not necessary during tuberculin treatment for the initial forms of pulmonary tuberculosis which are the most important cases for ambulant treatment.

**Objection on the  
Ground of  
Misuse.**

It is further objected that the recommendation of ambulant tuberculin treatment entails further consideration and that individual practitioners are not capable of conducting it. It is said that unsuitable tubercular cases and non-tubercular patients would be "injected," and suitable cases unsuitably treated with tuberculin; febrile patients would undertake drives and railway journeys of some hours to reach their doctor for the injections; others would be treated without exact control of the temperature being observed, or some would not take the temperature at all during the treatment; doctors would even supply their patients with tuberculin dilutions and syringes for their own use. We will not dispute the occurrence of these "outgrowths," but should prefer to designate them by the term "quackery" and condemn them most severely. But we believe these to be exceptional cases which, with a suitable and correctly performed ambulant cure, will decrease and disappear. In what province of medicine and applied science in general are there no such outgrowths, no mistakes, no errors in technique? Ought, therefore, all practitioners to be withheld or even forbidden tuberculin treatment on principle, merely because a few deny its value or misuse it?

**General Prac-  
titioners Capable of  
Conducting Am-  
bulant Treatment.**

The opponents of ambulant treatment undoubtedly over-estimate the difficulties of specific therapy of tuberculosis; in any case they are not so great that they cannot be overcome by all doctors, who daily have more difficult tasks put before them. Careful observation of the temperature, correct valuation of the subjective troubles, continuous control of the objective condition, of the pulse and the weight are the most important factors in tuberculin treatment, and at the same time their guiding lines. Do not let us forget that to-day we are only dealing with the mild method of administration, if possible without reaction, to gain success in which, in addition to the points just mentioned, time is the most important factor. The man who can take his time in increasing the dose and in the sequence of the injections, will never do any harm; and the general practitioner has this time, as the patient can quietly proceed with the duties of his calling.



### Selection of Cases.

As far as the selection of cases of tuberculosis for ambulant tuberculin treatment is concerned, we have expressed our opinion in detail in earlier chapters. We have a sufficiently high opinion of the conscientiousness of general practitioners to believe that before beginning the treatment they will make sure that active tuberculosis is present and in doubtful cases when necessary get the opinion of an experienced specialist, who can then decide whether ambulant tuberculin treatment shall be tried or whether it would be better to postpone or dispense with it altogether. According to our experience these are not difficulties but matters of course. Further, it is really evident that tuberculin will not be tried for psychotherapeutic reasons by the practitioner as an *ultimum remedium*, but that he and also the novice will limit their specific treatment to the initial stages of pulmonary tuberculosis and its favourable cases and more chronic forms. A case of phthisis accompanied by more or less continual fever is, even in the initial stage, no object for ambulant tuberculin treatment. It

### Unsuitable Conditions and Environment for Ambulant Treatment.

is true that we as sanatorium physicians value Koch's bacillary emulsion as the most excellent antifebrile remedy for tubercular fever, but attempts to reduce fever with tuberculin are not suitable for ambulant practice. In addition, harm will generally be done by tuberculin in the case of badly nourished tubercular patients. One tries, on the contrary, to fortify the organism by hyper-nutrition, to raise its resistance and power of assimilation. If, on economical grounds, hyper-nutrition is impossible or when attempted is unsuccessful, it is better to dispense with tuberculin; we do the same in the sanatorium. Where, also, there is no time for regular measurement of temperature, where a fresh air cure by night and rest for a few hours daily is impossible owing to restricted conditions of housing in the heart of a manufacturing quarter or to pressure of household duties, where hydrotherapeutic measures such as wet packs, friction, or baths are impracticable, where, lastly, there is no sense of personal hygiene and prophylaxis—then tuberculin injections alone will not prevent the advance of tubercular disease; therefore it is best to spare oneself and others the disappointment which must follow. We do not fear, however, that in such cases, where the pulmonary process is not too far advanced or too progressive, direct harm will be done by ambulant tuberculin treatment. But no good will be done, because the permanent



disadvantages and harmful effects of the surroundings outweigh all and leave no possible surplus of curative factors.

Thus for ambulant tuberculin treatment, just as for many surgical and gynæcological measures, there is a social indication and contra-indication which merit careful attention, as they exert a great influence on the final result of ambulant treatment.

And what about the capacity of the practitioner to conduct tuberculin cures? One must oneself have been a "mere" general practitioner fully to appreciate the offensiveness of criticism which, without reason, casts doubt upon the capacity and feeling of responsibility of the majority of the medical profession just because a few merely make haphazard injections instead of conducting a methodical course of tuberculin treatment. We regret the expression of such feeling on the part of high authorities, as it cannot conduce to the reputation of the pro-

**Necessity for Wide-  
spread Instruction  
in Tuberculin  
Treatment.**

fession. Deeds, too, are more useful than any amount of self-satisfied criticism! "Every physician *can* learn tuberculin treatment, and he *must* learn it." Based on this motto of Penzoldt's, let us enlist all sanatorium doctors to aid us as appointed guides for the therapeutic fight against tuberculosis. Let us continue to draw general practitioners into our sphere of work. Let us instruct all who require and demand information and a thorough understanding of specific treatment. In such a widespread disease there is work enough for us all. Let us try on our own initiative or with the help of the German Central Committee for the campaign against tuberculosis, or by post-graduate classes, to arrange courses of lectures, in which by demonstration of the technique of tuberculin treatment, by introduction of patients and by tuberculin charts it may be made evident to the general practitioner how simple the modern mild method really is. Two years' preparation, as has been demanded, is certainly not necessary to master the specific treatment. Such an extensive demand is quite impracticable and would make the treatment solely the affair of specialists; this is just what we want to avoid, for we should strive to combat tuberculosis universally, wherever it occurs, in every place, at all times, in every condition of life, at all ages, in short, everywhere that a focus is discovered.

In the first place, a thorough study of the theory is necessary in the literature of the subject. In every case a practical course would be an advantage, which could be run in connection with the existing University Holiday Courses and the medical courses



in the large towns, which are now already visited by thousands of doctors every year. When specific treatment becomes the common property of all hospitals, the observation of clinical cases and of out-patients will be easy for the majority of doctors. For medical students we confidently expect lectures on specific treatment to take a place in the curriculum. It would also be as well always to include in the final examination for medical degrees a few questions to show whether the candidate understands the salient features of the early recognition and treatment of tuberculosis, including the specific methods. The campaign against tuberculosis as a national disease is one of the most important duties of every far-seeing doctor who, as a cultured man, feels a share in the responsibility for the health of the nation. The realization that to-day the individual physician can play his part in this campaign with success, should cause every medical practitioner to spend part of his year's practice at a sanatorium or the department for tuberculosis of a hospital. But his chief assistance will always be the experience gained from his own patients, which is the right of every practitioner, provided he has the necessary theoretical knowledge.

In complete agreement with our ideas, **Ambulant Treatment Recommended by Many Authorities: Kayserling;** Kayserling, for example, the doctor at the Tuberculin Station of the National Insurance Offices in Berlin, looks upon it as an unquestionable duty to further the training of the practitioner in the use of tuberculin by giving him the opportunity of experience in treating cases in the various institutions for the treatment of diseases of the lung. "General practitioners must see that they are not again ousted from a sphere of work which they can and must master; they owe it, indeed, to science and to the health of the nation to take their share in the criticism of tuberculin treatment on the broad foundation of thorough knowledge and personal observation."

**F. Meyer;** F. Meyer [264], too, fully supports our view when he says: "Thus can tuberculin treatment become an important feature in the practice of the family doctor. It is very much to be hoped that the latter will not continue to feel that they are overstepping the proper limits of their work and refrain from all specific treatment. In the hands of a careful and experienced doctor, who also employs all other medical adjuvants for the treatment of tuberculosis, tuberculin treatment remains his most efficient weapon in the fight against the disease." Our standpoint has also been put forward in two



**Sorgo, Suesz, and Laub.**

noteworthy publications by the Austrian physicians, Sorgo and Suesz [296], and also Laub [297]. The former consider tuberculin a valuable remedy in the treatment of pulmonary tuberculosis, a remedy which should be used much more than formerly, and also in ambulant treatment with careful selection of the cases. They ask that due notice should be taken of tuberculin treatment in clinical text-books and in clinical instruction. Laub's successes were attained in ambulant treatment with patients who were pursuing their calling. He considers ambulant tuberculin treatment to be indicated in the case of many patients who are not in a position to visit a sanatorium. He closes his remarks with the words of Petruschky that "tuberculin, in fact, does all that can be reasonably expected from a diagnostic and therapeutic specific against tuberculosis." Also in England and America,

**Reports from England and America.**

very favourable results have been reported from ambulant tuberculin treatment. It is recommended by Clark, Fraser, Mayo, and Sutherland; Wilkinson records greater successes than those obtained by sanatorium treatment. Hawes and Floyd also warmly recommend ambulant treatment in commencing closed tuberculosis of children and adults, in advanced disease of very chronic course, in glandular, ocular, and urogenital tuberculosis.

**General Practitioners in Favour of Tuberculin in Private Practice.**

General practitioners themselves are also now demanding the right to use tuberculin in practice and energetically repudiate the opposite standpoint as retrogressive. It is in answer to this demand that lectures on the specific diagnosis and treatment of tuberculosis are given in the Berlin post-graduate course, that the well-known clinician, F. Kraus, advises practitioners not only to make the widest possible use of tuberculin diagnosis, but also to make general use of tuberculin treatment; that at the eighth session of the School for Social Medicine the Berlin group of the Society of German Doctors made the fundamental principles of the administration of tuberculin and its use in clinical practice accessible to the majority of medical men by means of lectures and demonstrations; that the Central Committee for post-graduate medical training in Prussia gives tuberculin treatment a place on the list of subjects for study; that this example is now followed by Munich, Hamburg, and other large cities; that the Prussian Department of Public Works and the Board of Managers of the State Railways of Saxony provide special courses in tuberculin treatment for the railway doctors; and that sanatoria, such as the



Fürth Sanatorium for Diseases of the Lung, train 80 per cent. of the doctors in their district in the practical use of tuberculin.

**Beninde.** In ever-increasing numbers, too, champions of our views step forth from the ranks of the practitioners and develop a method based on thorough study and personal experience which, in the main, agrees with our own. Thus Beninde [298], with the assistance of all the doctors of the district, started a tuberculin dispensary, which has been running successfully since November, 1908. Its object is to make early specific diagnosis and especially to treat gratis cases of tuberculosis which already received treatment with tuberculin in sanatoria. Private charity and the large contributions from the clubs of the district supply the necessary means, also free transit for the patients. Beninde, from the experience thus gained, now denies the assertion that ambulant treatment with tuberculin is a risky undertaking. "It is only necessary for the doctor to be thoroughly acquainted with the method and to draw the attention of the patients again and again to the necessity of carrying out strictly the directions given, especially as to taking the temperature. In the conditions of life in a small town and of a rural population, harm arising from the treatment of out-patients with tuberculin would certainly not remain unknown and would frighten the public away. But this has not been noticed by us hitherto. The doctors would certainly not continue to recommend such a dispensary to their patients. But hitherto there has been no question of so doing. On the contrary, we are just erecting three more such institutions in the district." Similar favourable experiences, even in tuberculosis of the second stadium, have just been recorded by Helwes [299] in Diepholz (Province of Hanover); here, too, it was the district doctor who introduced the ambulant treatment.

The erection of tuberculin dispensaries and their development is a sign of the direction which the struggle against tuberculosis is taking. But we look upon this even as a passing stage.

**Hillenberg.** Hillenberg [300], too, feels the same, as is evident from the concluding words of a work which well deserves reading:—

"The present position of the specific treatment of tuberculosis, owing to the favourable experience of very many great investigators, is such that the time seems to have come to pass it on from the sanatoria into general practice to a much larger extent than has hitherto been the case.

"An effort must be made to give an opportunity to all practitioners to become acquainted theoretically and practically with the conditions and fundamental principles of a specific treatment of



tuberculosis, by courses of lectures, easy to attend, held in very many places."

"Tuberculin treatment is not only to be used to cure individual cases, but is to be looked upon as one of the chief weapons in the fight against tuberculosis. It should be used in the prophylaxis of all those, especially the young, who suffer from latent, non-infectious tuberculosis, and especially in families in the vicinity of infectious invalids.

"All state and communal representatives of charitable and insurance societies are specially bound to do their share towards making the specific method accessible to all."

v. Leube.

The phthiseo-genetic demand that prophylaxis against tuberculosis in childhood must be our most important task in the fight against tuberculosis in general was recently emphasized by v. Leube [286]; and amongst other methods he recommended the use of tuberculin in diagnosis and treatment.

Such are the signs of the times. They are already perceptible in the proceedings of medical associations. Voituret [301], at the District Medical Association at Braunschweig, expressed his opinion that the practitioner must make greater use of tuberculin treatment than formerly and that in many cases he can often obtain striking success by its means. This need not stand in any rivalry to sanatoria or necessary operations, but should form a valuable adjuvant to their services. Many others of the Braunschweig practitioners were in full agreement with him. Were we to add the names of all the practitioners who, by word of mouth or in writing, have acquainted us with their reliance on tuberculin therapy, we should only tire the reader.

**Tuberculin must  
be the Common  
Property of  
all Practitioners.**

We content ourselves with the recognition that this is the sign of a realization of what is really necessary in the fight against tuberculosis. For tuberculin will not be used to its full advantage and its far-reaching importance realized if, excluding the sanatoria, merely a few doctors make use of it. No! Tuberculin must be an integral part of the medical equipment of every physician. It must be the Alpha and Omega of our diagnosis, prophylaxis, and therapy of tuberculosis. Then it will fulfil its destiny—to assist in the extirpation of the disease. And in conclusion we may hopefully give expression to the conviction that our conception of the far-reaching importance of the specific diagnosis and therapy of tuberculosis will soon be the common property of all medical men.



## Literature.

- [1] WEICHHARDT, W. Jahresberichte über die Ergebnisse der Immunitäts-  
forschung. Bd. 1906-1910, Stuttgart, Verlag von Enke.
- [2] MEYER, F. Folia Serologica. Bd. vii, Leipzig, 1911. Verlag von  
Klinkhard.
- [3] KOCH, R. Deutsche med. Wochenschrift, 1891, Nr. 3. Ebenda, 1890,  
Nr. 46a.
- [4] BUCHNER, H. Münch. med. Wochenschr., 1891, Nr. 3.
- [5] WASSERMANN and BRUCK. Deutsche med. Wochenschr., 1906, Nr. 12.
- [6] CHRISTIAN and ROSENBLAT. Münch. med. Wochenschr., 1908, Nr. 39.
- [7] LÜDKE. Münch. med. Wochenschr., 1908, Nr. 15, 16, 27. Beiträge  
zur Klinik der Tuberkul., Bd. vii, Heft 1.
- [8] BAUER. Verh. d. Ges. f. Kinderheilk. Kölner Naturforscher-Vers.,  
1908.
- [9] WEIL and NAKAJAMA. Münch. med. Wochenschr., 1906, Nr. 21.
- [10] MORGENROTH and RABINOWITSCH. Deutsche med. Wochenschrift,  
1907, Nr. 18.
- [11] ENGEL and BAUER. Münch. med. Wochenschr., 1908, Nr. 44.
- [12] LÜDKE and STURM. Münch. med. Wochenschr., 1912, Nr. 37.
- [13] CITRON. Berliner klin. Wochenschr., 1909, Nr. 51.
- [14] PAPPENHEIM. Folia haematologica, Bd. i, 1910. Verlag von Klink-  
hard, Leipzig.
- [15] HERTIG. Über die physiologischen Grundlagen der Tuberkulin-  
wirkung. Jena, 1891. Verlag von G. Fischer.
- [16] EHRLICH. International. Kongr. für Hygiene, 1903.
- [17] LANDMANN. Zentralblatt für Bakteriologie, Bd. xxvii, 1900.  
Hygienische Rundschau, 1898, Nr. 10 u. 1900, Nr. 8.
- [18] PICKERT. Deutsche med. Wochenschr., 1908, Nr. 52 u. 1909, Nr. 35.
- [19] LÖWENSTEIN. Deutsche med. Wochenschr., 1908, Nr. 52. Zeitschrift  
f. Tuberk., Bd. xv, Heft 4.
- [20] RUPPEL and RICKMANN. Zeitschr. f. Immunitätsforschung- u. experi-  
mentelle Therapie, Bd. vi, Heft 2 u. 3, 1910.
- [21] MEYER, F., and SCHMITZ, K. Deutsche med. Wochenschr., 1912,  
Nr. 42.
- [22] WOLFF-EISNER. Frühdiagnose u. Tuberkulose-Immunität. 1909.  
Verlag von Kabitzsch., Würzburg.
- [23] ZIELER. Münch. med. Wochenschr., 1910, Nr. 32.
- [24] SAHLI. Tuberkulinbehandlung und Tuberkuloseimmunität. Basel,  
1910. Verlag von B. Schwalbe and Co.
- [25] KRETZ. Beiträge zur Klinik der Tuberkulose, Bd. xii, Heft 3.
- [26] LÖWENSTEIN and RAPPAPORT. Deutsche med. Wochenschr., 1904.  
Nr. 23. Zeitschr. f. Tuberk., Bd. v, Heft 6, 1904.
- [27] v. PIRQUET. Klinische Studien über Vakzination und vakzinale  
Allergie. Wien, 1907. Verlag von Deuticke.
- [28] FRIEDBERGER. Med. Klinik, 1910, Nr. 13. Deutsche med. Wochen-  
schr., 1911, Nr. 11. Zeitschrift für Immunitätsforschung und ex-  
perimentelle Therapie, 1909-1911.
- [29] FRIEDBERGER, SZYMANOWSKI, KUMAGAI and ODAIRA, LURA. Zeitschrift  
f. Immunitätsforschung und experimentelle Therapie. Bd. xiv,  
Heft 4, 1912.
- [30] KÜHNE. Zeitschr. f. Biologie, 1892.
- [31] MATTHES. Deutsches Archiv f. klin. Medizin, 1895.



- [32] KREHL. Archiv f. exper. Pathol. u. Pharmakol., Bd. xxxvi, 1895.
- [33] ZUPNIK. Deutsches Archiv f. klin. Medizin. Bd. lxxvi, Heft 1-3, 1903.
- [34] PICKERT. Deutsche med. Wochenschr., 1909, Nr. 23.
- [35] BANDELIER. Deutsche med. Wochenschr., 1902, Nr. 20. Beiträge z. Klinik der Tuberkulose. Bd. ii, Heft 4.
- [36] ROEMER. Beiträge z. Klinik der Tuberkulose, 1910. Bd. xvii, Heft 3. Tuberculosis, 1910, Nr. 4.
- [37] KLINGMÜLLER. Archiv f. Dermatolog. u. Syphil. Bd. lxxix, Heft 1 und 2.
- [38] RUPPEL. Münch. med. Wochenschr., 1910, S. 2303.
- [39] KOCH, R. Deutsche med. Wochenschr., 1901, Nr. 48.
- [40] BANDELIER. Zeitschr. f. Hygiene und Infektionskrankheiten. Bd. xliii, 1903.
- [41] WRIGHT and DOUGLAS. Proceedings of the Royal Society, vol. lxxii, Nr. 433, 1903, and vol. lxxiv, Nr. 499, 1904.
- [42] TURBAN and BAER. Beiträge z. Klinik der Tuberkulose, Bd. x, Heft 1. Münch. med. Wochenschr., 1908, Nr. 38.
- [43] NEUFELD. Berliner klin. Wochenschr., 1908, Nr. 21.
- [44] LOEWENSTEIN. Zeitschr. f. Hygiene u. Infektionskrankheiten, Bd. lv. Zeitschr. f. Tuberk., Bd. x, Heft 1. Deutsche med. Wochenschr., 1907, Nr. 43.
- [45] MORLAND. Über die klinische Bedeutung der Opsonine. Inaug. Dissertation. Samaden, 1908.
- [46] KRUSE. Flügges Handbuch der Mikroorganismen. Fischer, Jena.
- [47] MÜLLER, P. TH. Vorlesungen über Infektion und Immunität. Jena, 1909. Verlag von G. Fischer.
- [48] BÖHME. Münch. med. Wochenschr., 1909, Nr. 22 u. 23.
- [49] KRAUS and HÖFER. Deutsche med. Wochenschr., 1912, Nr. 26.
- [50] ENGEL and BAUER. Münch. med. Wochenschr., 1908, Nr. 44.
- [51] JOCHMANN and MÖLLERS. Veröffentlichung der Robert Koch-Stiftung, Heft 3.
- [52] MÖLLERS. Zentralblatt f. Bakteriologie, Parasitenkunde u. Infektionskrankh., 1912, Bd. liv, Beiheft. Deutsche med. Wochenschr., 1912, Nr. 16.
- [53] v. PIRQUET. Klinische Studien über Vakzination und vakzinale Allergie. Wien, 1907. Verlag von Deuticke. Handbuch der Technik und Methodik der Immunitätsforschung. Jena, 1908. Verlag von G. Fischer. Wiener klin. Wochenschr., 1908, Nr. 17. Tuberculosis, vol. vii, Nr. 6. Deutsche med. Wochenschr., 1908, Nr. 30.
- [54] GANGHOFNER. Wien. klin. Wochenschr., 1908, Nr. 41.
- [55] ZIELER. Münch. med. Wochenschr., 1908, Nr. 32. Deutsche med. Wochenschr., 1911, Nr. 45.
- [56] DAELS. Mediz. Klinik, 1908, Nr. 2.
- [57] BUMM. Sitzungsbericht des Ausschusses des Deutschen Zentralkomitees. Mai, 1910.
- [58] ROLLY. Münch. med. Wochenschr., 1911, Nr. 24.
- [59] ROEPKE. Beiträge zur Klinik der Tuberkulose, Bd. ix, Heft 3 und Bd. xi, Heft 2.
- [60] ERLANDSEN and PETERSEN. Beiträge zur Klinik der Tuberkulose, Bd. xvi, Heft 3.
- [61] ERLANDSEN. Beiträge zur Klinik der Tuberkulose, Bd. xviii, Heft 3.
- [62] DITTHORN and SCHULTZ. Deutsche med. Wochenschr., 1908, Nr. 28.
- [63] SCHELLENBERG. Zeitschr. f. Tuberkulose, Bd. xviii, Heft 2.
- [64] DETRE. Wien. klin. Wochenschr., 1908, Nr. 6 u. Nr. 41.
- [65] MORO and DOGANOFF. Wien. klin. Wochenschr., 1907, Nr. 31.
- [66] MORO. Münch. med. Wochenschr., 1908, Nr. 5. Beiträge zur Klinik der Tuberkulose, Bd. xii, Heft 2.
- [67] LIGNIÈRES. Zentralbl. f. Bakteriolog., Bd. lxxiv, Heft 4.
- [68] LAUTIER. Mitteilung in der Société de Biolog. in Paris, v. 28, i, 1908.
- [69] MENDEL. Mediz. Klinik, 1908, Nr. 12.
- [70] MANTOUX and ROUX. Zit. nach Münch. med. Wochenschr., 1908, Nr. 40.
- [71] ENGEL. Deutsche med. Wochenschrift, 1911, Nr. 36.
- [72] MANTOUX. Presse Médicale, 1910, Nr. 2.



- [73] MONTI. Wiener med. Wochenschr., 1912, Nr. 7.
- [74] RÖMER and JOSEPH. Beiträge zur Klinik der Tuberkulose, Bd. xiv, Heft 1.
- [75] RÖMER. Beiträge zur Klinik der Tuberkulose, Bd. xii, Heft 1.
- [76] ZSCHOCKE. Die Intrakutanreaktion bei Tuberkulose von Rind und Schwein. Veter.-med. Dissertation. Dresden, 1909.
- [77] ESCH. Münch. med. Wochenschr., 1912, Nr. 39.
- [78] CALMETTE. Acad. des Sciences. Sitz., v. 17, juin, 1907, Sem. méd., 1907.
- [79] WOLFF-EISNER. Berliner klin. Wochenschr., 1907, Nr. 22. Beiträge zur Klinik der Tuberk., Bd. ix, Heft 1.
- [80] CITRON. Deutsche med. Wochenschr., 1908, Nr. 8.
- [81] KLIMMER and KIESSIG. Monatsch. f. prakt. Tierheilk., Bd. xx, Heft 3.
- [82] WIENS and GÜNTHER. Münch. med. Wochenschr., 1908, Nr. 36.
- [83] M. WOLFF. Berl. klin. Wochenschr., 1908, Nr. 6.
- [84] WOLFF-EISNER. Münch. med. Wochenschr., 1909, Nr. 44. Frühdiagnose und Tuberkulose-Immunität. Würzburg, 1909. A. Stubers Verlag.
- [85] SCHRUMPF. Münch. med. Wochenschr., 1908, Nr. 43.
- [86] R. KOCH. Deutsche med. Wochenschr., 1890, Nr. 7.
- [87] HOLLMANN. Beiträge zur Klinik der Tuberkulose, Bd. xxi, Heft 2.
- [88] BECK. Deutsche med. Wochenschr., 1899, Nr. 5.
- [89] R. KOCH. Deutsche med. Wochenschr., 1901, Nr. 48.
- [90] LÖWENSTEIN and KAUFMANN. Zeitschr. f. Tuberk., Bd. x, Heft 1.
- [91] BANDELIER. Beiträge z. Klinik d. Tuberk., Bd. vi, Heft 1.
- [92] ROEPKE. Beiträge z. Klinik d. Tuberk., Bd. i, Heft 3. Zeitschr. f. Tuberk., Bd. x, Heft 5.
- [93] FRANZ. Wiener klin. Wochenschr., 1909, Nr. 28.
- [94] HAMMER. Beiträge z. Klinik d. Tuberk., Bd. i, Heft 4.
- [95] JUNKER. Beiträge z. Klinik d. Tuberk. Bd. 6, Heft 4.
- [96] BULLE. Zeitschr. f. Bahn- u. Bahnkassenärzte, 1909, Nr. 11.
- [97] SAATHOFF. Münch. med. Wochenschr., 1909, Nr. 40 and 1910, Nr. 33.
- [98] REZNICEK. Beiträge zur Klinik der Tuberkulose, Bd. xx, Heft 2.
- [99] SCHÜTZ. Verhandl. des 27. Kongr. für innere Medizin. Wiesbaden, 1910.
- [100] ENGEL. Beiträge z. Klinik der Tuberkulose, Bd. xiii, Heft 3.
- [101] BINSWANGER. Arch. f. Kinderheilk., 1906, Bd. xl, Heft 1-4.
- [102] ESCHERICH. Jahrbuch f. Kinderheilk., Bd. xxxiii.
- [103] REUSCHEL. Münch. med. Wochenschr., 1908, Nr. 7.
- [104] HAMBURGER. Wiener klin. Wochenschr., 1908, Nr. 12.
- [105] PENZOLDT. Verhandlungen des 27. Kongresses für innere Medizin. Wiesbaden, 1910.
- [106] KAMMERER. Inaugural-Dissertation. Tübingen, 1904.
- [107] OTTEN. Medizinische Klinik, 1910, Nr. 28.
- [108] v. ROMBERG. Verhandlungen des 27. Kongr. für innere Medizin. Wiesbaden, 1910.
- [109] WALTERHÖFER. Beiträge zur Klinik der Tuberkulose, Bd. xxi, Heft 2.
- [110] KRÖNIG. Deutsche Klinik, Bd. xi.
- [111] BLÜMEL. Münch. med. Wochenschr., 1908, Nr. 30.
- [112] ULRICI. Beiträge zur Klinik der Tuberkulose. 3. Supplement-Band.
- [113] KÖGEL. Beitr. z. Klinik der Tuberkulose, Bd. xxiii, Heft 1.
- [114] HEINEMANN. Münch. med. Wochenschr., 1908, Nr. 11.
- [115] NEISSER, A. Amtliche Berichte: Die Wirksamkeit des Kochschen Heilmittels gegen Tuberkulose. Berlin, 1891. Verlag von Springer.
- [116] FRÄNKEL, B. Amtliche Berichte. Berlin, 1891.
- [117] STARGARDT. Zeitschrift für Augenheilkunde, Bd. xxii, Heft 1.
- [118] v. HIPPEL. Amtliche Berichte. Berlin, 1891.
- [119] HESS, C. Med. Klinik, 1910, Nr. 33.
- [120] HEINE. Med. Klinik, 1912, Nr. 44 und 45.
- [121] AUGSTEIN. Zeitschr. für Bahnärzte, 1911, Nr. 6.
- [122] IGERSCHEIMER. Deutsche med. Wochenschrift, 1912, Nr. 37. Sammelreferat S. 1740.
- [123] DAVIDS. Sitzungsbericht der Med.-naturwissenschaftl. Ges. in Münster. 8 Juni, 1909. v. Graefes Archiv für Ophthalmologie, Bd. lxix, Heft 2.
- [124] SCHOELER, F. Klinisches Jahrbuch, Bd. xxii, 1909.



- [125] NEISSER, A. Med. Klinik, 1909, Nr. 41, p. 1567.
- [126] HEUCK. Münch. med. Wochenschrift, 1909, Nr. 31, S. 1621.
- [127] WILMS. Deutsche med. Wochenschr., 1911, Nr. 36. Deutsche Zeitschr. f. Chirurg., Bd. cxv, Heft 5-6.
- [128] ZOEPPRITZ. Mitteilungen a. d. Grenzgeb. d. Medizin u. Chirurgie, Bd. xix, Heft 3.
- [129] WALDSTRÖM. Zeitschrift f. orthopädische Chirurgie, Bd. xxvi, Heft 4.
- [130] WOLFSOHN. Med. Klinik, 1910, Nr. 37.
- [131] HOHLWEG. Münch. med. Wochenschr., 1911, Nr. 51.
- [132] STERN, R. Zeitschr. f. Geburtshilfe u. Gynäkol., Bd. lxvi, Heft 3.
- [133] NECKER and PASCHKIS. Wiener klin. Wochenschr., 1908, Nr. 40.
- [134] CASPER. Sitzungsbericht des Vereins für innere Medizin in Berlin, Jan. 20, 1908.
- [135] KARO. Münch. med. Wochenschr., 1904, Nr. 37.
- [136] HÖRMANN. Münch. med. Wochenschr., 1908, Nr. 26.
- [137] BIRNBAUM. Das Kochsche Tuberkulin in der Gynäkologie und Geburtshilfe. Berlin, 1907. Verlag von Springer. Zentralbl. f. Gynäk., 1907, Heft 39.
- [138] PROCHOWNIK. Münch. med. Wochenschr., 1909, Nr. 20, S. 1047.
- [139] SCHLIMPERT and ZOEPPRITZ. Verhandl. der deutsch. Ges. f. Gynäkologie in München, 1911.
- [140] V. FRANQUÉ. Med. Klinik, 1911, Nr. 27.
- [141] HEIMANN. Zeitschr. f. Geburtshilfe u. Gynäkologie, 1910, Bd. lxvi, Heft 3.
- [142] HAMBURGER. Wiener klin. Wochenschr., 1907, Nr. 36.
- [143] ERHLICH and GUTTMANN. Deutsche med. Wochenschr., 1891.
- [144] LICHTHEIM. Klinisches Jahrbuch, 1891. Ergänzungsbd. Deutsche med. Wochenschr., 1891.
- [145] AUFRECHT. Deutsches Arch. f. klin. Med., 1891, Bd. 49.
- [146] BIEDERT. Vereinig. niederrhein.-westfäl. u. südwestdeutscher Kinderärzte in Wiesbaden, 1909, Diskuss.-Bemerkung.
- [147] PETRUSCHKY. Berl. klin. Wochenschr., 1891. Sitzungsber. d. Königsberger Vereins f. wissenschaftl. Heilk.
- [148] GOETSCH. Deutsche med. Wochenschr., 1901, Nr. 25.
- [149] BANDELIER. Beiträge z. Klinik d. Tuberk. u. spez. Tuberkulose-Forschung, Bd. xv, Heft 1.
- [150] JOCHMANN. Deutsche med. Wochenschr., 1910, Nr. 21.
- [151] JACOB. Deutsche med. Wochenschr., 1904, Nr. 26-28.
- [152] LEVIN. Deutsche med. Wochenschr., 1904, Nr. 44.
- [153] KAPRALIK and H. VON SCHROETTER. Wiener klin. Wochenschr., 1904, Nr. 21 u. 22.
- [154] BANDELIER. Beiträge z. Klinik d. Tuberk., Bd. vi, Heft 1.
- [155] HUHS. Beiträge z. Klinik d. Tuberk., Bd. vii, Heft 1.
- [156] B. MÖLLERS and HEINEMANN. Deutsche med. Wochenschr., 1911, Nr. 40.
- [157] KRAUSE, A. Zeitschr. f. Tuberk., Bd. x, Heft 6.
- [158] MÜNCH. Beiträge z. Klinik d. Tuberk. u. spez. Tuberkulose-Forschung., Bd. xvii, Heft 2.
- [159] POEPPELMANN. Berl. klin. Wochenschr., 1910, Nr. 42.
- [160] ROLLY. Münch. med. Wochenschr., 1910, Nr. 16.
- [161] PENZOLDT. Deutsches Archiv f. klin. Medizin, Bd. c, Heft 1 u. 2.
- [162] BANDELIER. Deutsche med. Wochenschr., 1898, Nr. 50 u. 51.
- [163] SAHLI. Korrespondenzbl. f. Schweizer Ärzte, 1906, Nr. 12 u. 13.
- [164] —. Beiträge z. Klinik d. Tuberk. u. spez. Tuberkulose-Forschung, Bd. x, Heft 4.
- [165] VAUGHAN. Zeitschr. f. Immunitätsforschung u. experiment. Therap., Bd. i, Heft 2.
- [166] PETRUSCHKY. Vorträge z. Tuberkulose-Bekämpfung. Leipzig, 1900. Verlag von F. Leineweber.
- [167] —. Über Heilstätten- und Tuberkulin-Behandlung in gegenseitiger Ergänzung. Leipzig, 1901. Verlag von F. Leineweber.
- [168] —. Ergebnisse der inneren Medizin und Kinderheilkunde, 1912, Bd. ix.
- [169] KRAEMER. Das Prinzip der Dauerheilung der Tuberkulose. Tübingen. 1904. Verlag von F. Pietzcker.



- [170] SCHRÖDER. Beiträge z. Klinik d. Tuberk. u. spez. Tuberkulose-Forschung, Bd. xxiii, Heft 1.
- [171] JOCHMANN. Deutsche med. Wochenschr., 1910, Nr. 21.
- [172] RUPPEL. Über Tuberkulin und andere spez. Präparate zur Erkennung und Bekämpfung der Tuberkulose. Berlin, 1909. Verlag von Gebrüder Borntraeger.
- [173] JOCHMANN and MÖLLERS. Deutsche med. Wochenschr., 1911, Nr. 28.
- [174] KOCH, R. Deutsche med. Wochenschr., 1897, Nr. 14.
- [175] KRAUSE, F. Münch. med. Wochenschr., 1905, Nr. 52.
- [176] KLEBS. Wiener med. Wochenschr., 1891, Nr. 15.
- [177] —. Zentralbl. f. Bakteriolog., 1896, xx.
- [178] —. Deutsche med. Wochenschr., 1907, Nr. 15.
- [179] KLEBS. Deutsche med. Wochenschr., 1908, Nr. 3. (Vortrag im Berliner Verein f. inn. Med.)
- [180] BÉRANECK. Compt. rend. de l'acad. des sciences, 1903. Tome 137. Revue méd. de la Suisse romande, 1905, Nr. 10. Int. Tub.-Kongr., 1905.
- [181] CARL SPENGLER. Deutsche med. Wochenschr., 1904, Nr. 31; 1905, Nr. 31 u. 34; 1907, Nr. 9.
- [182] —. Zentralbl. f. Bakteriolog., Parasitenkunde u. Infektionskrankheiten, 1907, Bd. xlv.
- [183] SCHROEDER. Beiträge z. Klinik d. Tuberk. u. spez. Tuberk.-Forsch. Bd. xi, Heft 2.
- [184] MIETZSCH. Beiträge z. Klinik d. Tuberk. u. spez. Tuberk.-Forschung, Bd. xii, Heft 3.
- [185] CARL SPENGLER. Wiener klin. Rundschau, 1906, Nr. 33.
- [186] BONOME. Zentralbl. f. Bakteriolog. Parasitenkunde u. Infektionskrankheiten, 1907, Bd. xliii, Heft 4.
- [187] V. SZABÓKY. Zeitschr. f. Tuberk., Bd. xiv, Heft 1.
- [188] WEBER and DIETERLEN. Tuberkulose-Arbeiten aus dem Kaiserl. Gesundheitsamte. Berlin. Verlag von Jul. Springer, 1910, Heft 10.
- [189] KRAUSE, A. Zeitschr. f. Tuberk., 1907, Bd. xi.
- [190] LOEWENSTEIN. Zeitschr. f. Hyg. u. Infektionskrankh., 1905, Bd. li. Zeitschr. f. Tuberk., 1906, Bd. x, Heft 1.
- [191] ROTHCHILD. Zeitschr. f. Tuberk., 1908, Bd. xii, Heft 5. Deutsche med. Wochenschr., 1909, Nr. 21.
- [192] ROSENFELD, F. Mediz. Korrespondenzblatt d. Württemberg. ärztl. Landesvereins, 1909, Nr. 39.
- [193] DENYS. Le bouillon filtré du bacille de la tuberculose. Louvain, Paris, 1905.
- [194] GABRILOWITSCH. Zeitschr. f. Tuberk., 1907, Bd. xi, Heft 1.
- [195] GORDON. Deutsche med. Wochenschr., 1910, Nr. 38.
- [196] ROSENBAUM. Deutsche med. Wochenschr., 1910, Nr. 33 u. 34; 1912, Nr. 12 u. 13.
- [197] KOHLER and PLAUT. Zeitschr. f. klin. Med., 1912, Bd. lxxiv, Heft 3 u. 4.
- [198] STOLZENBURG. Bericht über die Fürstlich Hohenlohe'sche Lungenheilstätte Slawentzitz für die Jahre 1910 und 1911.
- [199] SCHAEFER. Zeitschr. f. Tuberk., 1911, Bd. xviii, Heft 2.
- [200] DITTHORN and SCHULTZ. Zeitschr. f. Immunitätsforschung u. experiment. Therapie, 1909. Bd. ii, Heft 5.
- [201] SCHULTZ. Berl. klin. Wochenschr., 1909, Nr. 38.
- [202] AMREIN. Beiträge z. Klinik d. Tuberk. u. spez. Tuberkulose Forschung, 1912, Bd. xxiii, Heft 2.
- [203] CANTANI. Zeitschr. f. Hyg. u. Infektionskrankh., 1909, Bd. lxiii, Heft 1.
- [204] TURMANN. Münch. med. Wochenschr., 1909, Nr. 30.
- [205] NOGUCHI. Zentralbl. f. Bakteriolog., Parasitenkunde und Infektionskrankh., 1909, Bd. lii, Heft 1.
- [206] ZEUNER. Zentralbl. f. Bakteriolog., Parasitenkunde u. Infektionskrankh., 1909, Bd. l, Heft 1. Zeitschr. f. Tuberk., 1909, Heft 2.
- [207] MARXER. Zeitschr. f. Immunitätsforschung u. experiment. Therapie, 1911, Bd. x, Heft 1 u. 2, u. Bd. xi, Heft 5.
- [208] ZEUNER. Allgem. Med. Zentral-Zeitung, 1912, Nr. 33.
- [209] HAENTJENS. Zeitschr. f. Tuberk., 1907, Bd. xi, Heft 3 u. 4. Tuberkulosis, 1909, vol. 8, Nr. 6.



- [210] BUCHNER and HAHN. Münch. med. Wochenschr., 1897, Nr. 48.
- [211] WELEMINSKY. Berl. klin. Wochenschr., 1912, Nr. 28.
- [212] PACHNER. Beiträge z. Klinik d. Tuberk. u. spez. Tuberkulose-Forschung, Bd. xxv, Heft 1.
- [213] MCFADYEAN. The Journal of Comparative Pathology and Therapeutics, 1901 and 1902.
- [214] MOELLER. Handbuch der Therapie der chronischen Lungenschwindsucht von Schroeder und Blumenfeld, Leipzig, 1904. Verlag von Joh. Amb. Barth.
- [215] KLEBS. Virchows Archiv f. pathol. Anat. u. Physiol. u. f. klin. Med., 1908, Bd. clxxxiv, Beiheft. Sitzung d. Berl. med. Gesellsch. v. 16. Dez., 1907. Deutsche Ärzteztg., 1908, Nr. 20.
- [216] —. Berl. klin. Wochenschr., 1909, Nr. 33 u. 34.
- [217] FRIEDMANN. Zeitschr. f. Tuberk., Bd. iv. Deutsche med. Wochenschr., 1903, Nr. 50 u. 1904, Nr. 5 u. 46.
- [218] —. Sitzung der Berl. med. Gesellschaft vom 6 u. 13. Nov., 1912.
- [219] CALMETTE and GUÉRIN. Acad. des scienc., 11, vi, 06.
- [220] WEBER, A. and TITZE. Tuberk.-Arbeiten aus dem Kais. Gesundheitsamte, Berlin. Verlag von Jul. Springer, 1907. Heft 7; 1908, Heft 9; 1910, Heft 10.
- [221] VALLÉE. Annales de l'Institut Pasteur, August, 1909.
- [222] V. BAUMGARTEN. Berlin. klin. Wochenschr., 1904, Nr. 43. Arb. a. d. patholog. Institut Tübingen, 1910, Bd. vii.
- [223] KOCH, SCHÜTZ, NEUFELD, MIESSNER. Zeitschr. f. Hyg. u. Infektionskrankh., 1905, Bd. li.
- [224] KLEMPERER, F. Zeitschr. f. klin. Med., Bd., lvi.
- [225] ROEMER and JOSEPH. Beiträge z. Klinik d. Tuberk. u. spez. Tuberkulose-Forschung, Bd. xvii.
- [226] ROEMER. Beiträge z. Klinik d. Tuberk. u. spez. Tuberkulose-Forschung, Bd. xxii, Heft 3.
- [227] KLIMMER. Zeitschr. f. Tuberk., 1908, Bd. xii, Heft 5 u. 6. Bericht über das Hyg. Institut u. die Seuchenversuchsanstalt. Sonderabdruck aus dem Berichte über die Königl. Tierärztliche Hochschule zu Dresden auf das Jahr 1909, Dresden, 1910. Schweizer Archiv für Tierheilkunde, 1910, Heft 6.
- [228] BARTEL, J. Vortrag, gehalten auf dem VI. Internat. Tuberk.-Kongress in Washington, 1908.
- [229] LEVY and KRENCKER. Zeitschr. f. Immunitätsforschung u. experiment. Therapie, 1909, Bd. iv.
- [230] STEFFEN. Münch. med. Wochenschr., 1910, Nr. 16.
- [231] DEYCKE and RESCHAD BEY. Deutsche med. Wochenschr., 1905, Nr. 13 u. 14 u. 1907, Nr. 3. Sitzung der Biolog. Abteilung des Ärzte-Vereins Hamburg, 22 x, 1907. Lepra. Bibliotheca internationalis, 1907, vol. vii, Fasc. 3.
- [232] DEYCKE and MUCH. Med. Klinik. 1908, Nr. 40.
- [233] MUCH. Münch. med. Wochenschr., 1909, Nr. 36.
- [234] DEYCKE and MUCH. Münch. med. Wochenschr., 1909, Nr. 39.
- [235] BORISSJACK, SIEBER and METALNIKOW. Zeitschr. f. Immunitätsforschung u. experiment. Therapie, Bd. xii, Heft 1.
- [236] MARAGLIANO. Tuberculosis, 1906, Bd. v.
- [237] MARMOREK. Berliner klin. Wochenschr., 1903, Nr. 48. Med. Klinik, 1906, Nr. 3. Sitzung d. Berliner med. Gesellsch., v. 8, v. 1907.
- [238] ELSÄSSER, M. Deutsche med. Wochenschr., 1905, Nr. 48 u. 1907, Nr. 51.
- [239] ELSÄSSER, F. A. Zeitschr. f. Tuberk., 1907, Bd. xi, Heft 4.
- [240] FREY. Münch. med. Wochenschr., 1904, Nr. 44. Berliner klin. therapeut. Wochenschr., 1905, Nr. 42. Vers. Deutsch. Naturforsch. u. Ärzte, 1907. Zeitschr. f. Tuberk., 1908, Bd. xiii, Heft 2.
- [241] KÖHLER. Zeitschr. f. Tuberk., 1908, Bd. xiii, Heft 2 u. 1910, Bd. xvi, Heft 6.
- [242] KAUFMANN. Beiträge z. Klinik d. Tuberk. u. spez. Tuberkulose-Forschung, Bd. xi, Heft 3.
- [243] TURBAN. VIII Internat. Tuberk.-Konferenz zu Stockholm, 1909.
- [244] MONOD. Ref. in Zeitschr. f. Tuberk., 1907, Bd. x.



- [245] MARMOREK. XI Congrès français de médecine, Paris, Octobre, 1910. La presse méd., 1910, Nr. 89.
- [246] SOBOTTA. Zeitschr. f. Tuberk., 1911, Bd. xvii, Heft 6.
- [247] MARMOREK. Berliner klin. Wochenschr., 1902.
- [248] ARONSON. Berliner klin. Wochenschr., 1902.
- [249] MENZER. Münch. med. Wochenschr., 1903, Nr. 25 u. 26. Berlin, 1904. Verlag von G. Reimer.
- [250] ZANGEMEISTER. Deutsche med. Wochenschr., 1906, Nr. 27. Berliner klin. Wochenschr., 1909, Nr. 20.
- [251] SCHROEDER. Beiträge z. Klinik d. Tuberk. u. spez. Tuberkulose-Forschung, Bd. xii, Heft 3.
- [252] SCHROEDER, KAUFMANN and KÖGEL. Beiträge z. Klinik d. Tuberk. u. spez. Tuberkulose-Forschung, Bd. xxiii, Heft 1.
- [253] CARL SPENGLER. Deutsche med. Wochenschr., 1908, Nr. 38.
- [254] CARL SPENGLER'S Tuberkulose und Syphilis-Arbeiten, Davos, 1911. Verlag von H. Erfurt.
- [255] HERZBERG. Münch. med. Wochenschr., 1909, Nr. 5.
- [256] ROEPKE. Deutsche med. Wochenschr., 1909, Nr. 42.
- [257] BANDELIER. Deutsche med. Wochenschr., 1909, Nr. 42.
- [258] KRAUS, F. Zeitschr. f. ärztl. Fortbildung, 1911, Nr. 22 u. 23.
- [259] HAMMER. Münch. med. Wochenschr., 1906, Nr. 48. Beiträge z. Klinik d. Tuberk., Bd. vii.
- [260] MARYAN FRANKE. Beiträge z. Klinik d. Tuberk. u. spez. Tuberkulose-Forschung, Bd. xi, Heft 3.
- [261] GRAU. Deutsches Archiv f. klin. Med., Bd. cl, Heft 1 u. 2.
- [262] BLUMENFELD. Zeitschr. f. Laryngologie, Rhinologie u. ihre Grenzgebiete, 1911, Bd. iv, Heft 4.
- [263] ED. MEYER. Verhandlungen des Vereins deutscher Laryngologen. Würzburg, 1911. Verlag von C. Kabitzsch.
- [264] MEYER, F. Therapeutische Monatshefte, August, 1911.
- [265] CASPER. Berliner klin. Wochenschr., 1909, Nr. 22.
- [266] KARO. VIII Internat. Tuberk.-Konferenz, Stockholm, 1909. 32. Versammlung d. Balneologischen Gesellschaft, Berlin, 1911. Med. Klinik, 1911, Nr. 26.
- [267] MANTOUX. La presse méd., 1910, Nr. 76.
- [268] GRÄFENBERG. Mon. f. Geb. u. Gynäk., 1910, Bd. xxxi.
- [269] v. HIPPEL, A. Archiv f. Ophthalmologie, Bd. lix, Heft 1.
- [270] DAVIDS. Klin. Monatsbl. f. Augenheilk., 1909, Bd. xlvii (Neue Folge. Bd. vii) v. Graefes Archiv f. Ophthalmologie, 1908, Bd. lxxix, Heft 2.
- [271] SCHEUERMANN. Zeitschr. f. Augenheilk., 1909, Bd. xxii, Heft 1.
- [272] SCHNAUDIGEL. Sitzung d. Ärztl. Vereins in Frankfurt-a.-M. vom 21. xi, 11. Ref. Münch. med. Wochenschr., 1911, Nr. 3.
- [273] v. HERRENSCHWAND. Archiv f. Augenheilk., Bd. lxxviii, Heft 1.
- [274] JUNIUS. Zeitschr. f. Augenheilk., 1909, Bd. xxi, Heft 5.
- [275] VOSS. Sitzung d. wissensch. Vereinigung am städt. Krankenh. zu Frankfurt-a.-M. vom 4. x, 1910. Ref. Münch. med. Wochenschr., 1910, Nr. 46.
- [276] DAUTWIZ. Beiheft z. Med. Klinik, 1908, Heft 9.
- [277] NEUMANN, W. Beiträge z. Klinik d. Tuberk. u. spez. Tuberk.-Forschung, Bd. xvii, Heft 1.
- [278] LENZMANN. Beiheft z. Med. Klinik, 1909, Heft 2.
- [279] BUNGART. Deutsche Zeitschr. f. Chirurgie, 1912, Bd. cxiii.
- [280] BANDELIER. Deutsche med. Wochenschr., 1898, Nr. 50 u. 51.
- [281] HOFFA. Berliner klin. Wochenschr., 1906, Nr. 8 u. 44. Deutsche med. Wochenschr., 1907, Nr. 10.
- [282] GLAESSNER. Zeitschr. f. Tuberk. 1910, Bd. xvi, Heft 5.
- [283] ENGEL. Beiträge z. Klinik d. Tuberk., 1907, Bd. vii.
- [284] SCHLOSSMANN. Deutsche med. Wochenschr., 1909, Nr. 7.
- [285] ROHMER. Archiv f. Kinderheilkunde, Bd. lv.
- [286] v. LEUBE. Münch. med. Wochenschr., 1912, Nr. 31 u. 32.
- [287] KRAUSE, A. Zeitschr. f. Stadthygiene, 1910.
- [288] CITRON. Deutsche med. Wochenschr., 1912, Nr. 20.
- [289] KLEMPERER, F. Die Therapie der Gegenwart, 1909, Heft 1 u. 2.
- [290] SCHRÖDER. Beiträge z. Klinik d. Tuberk., Bd. xxiii, Heft 1.
- [291] MEISSEN. Beiträge z. Klinik d. Tuberk. III Supplement-Band.



- [292] HAUPT. Beiträge z. Klinik d. Tuberk., Bd. xxiii, Heft 4.
- [293] KRUSIUS. Deutsche med. Wochenschr., 1912, Nr. 17.
- [294] KRAEMER. Mediz. Korrespondenzblatt d. Württemb. ärztl. Landesvereins, 1906.
- [295] NEUFELD. Spezifische Mittel. Denkschr. d. deutschen Zentral-Komitees zur Errichtung von Heilstätten für Lungenkranke. Berlin, 1905.
- [296] SORGO and SUESZ. Wiener klin. Wochenschr., 1911, Nr. 1.
- [297] LAUB. Wiener klin. Wochenschr., 1911, Nr. 1.
- [298] BENINDE. Gesundheit, 1909, Nr. 18. Deutsche med. Wochenschr., 1910, Nr. 23.
- [299] HELWES. Zeitschrift für Medizinalbeamte, 1912. Berichte, S. 108.
- [300] HILLENBERG. Vierteljahrsschrift für gerichtliche Medizin und öffentliches Sanitätswesen. 3. Folge, xxxvii, 1.
- [301] VOITURET. Med. Klinik, 1912, Nr. 46, p. 1886.



# Index.

- ACTION, difference of, in Koch's tuberculin, 135-139  
 —, non-specific, in the tuberculin reaction, 22-23  
 Active immunization, 158-159  
 — —, methods of, on the lines of Jenner and Pasteur, 197-205  
 — —, remedies used in, 159-208  
 Agglutinins, 29-30  
 Albumose-free tuberculin, in diagnosis, 38, 69  
 — —, in treatment, 164-167  
 Amboceptor theory, 18-19  
 Ambulant use of tuberculin, diagnosis, 4, 44, 48, 53, 67, 68, 79, 80, 95, 96, 277  
 — —, treatment, 278-294  
 Anaphylaxis in tuberculin diagnosis, 75  
 Antibodies, as curative factors, 28-36  
 —, complement fixing, 36  
 Antiphthisin (Klebs'), 178  
 Antiphymatol, 203-204  
 Antitoxins, 28-29  
 Antitubercular serum (Marmorek's), 211-214  
 Arsenical tuberculin, 193  
 Auricular reaction, 92  
 Auto-antigens, 195  
  
 BACILLARY emulsion, 169-173  
 — —, sensitized, 173-175  
 — —, specific, 185  
 Bacteriolysins, 35-36  
 Bacteriotropins, 35  
 Béranek's tuberculin, 178-180  
 Bones, tuberculosis of the, specific treatment of, 265-269  
 — — —, tuberculin diagnosis in, 121-123  
 Bovine bacillary emulsion, 173, 182  
 Bovine old tuberculin, in diagnosis, 48-49, 70  
 — — —, in treatment, 164, 182  
 — tuberculin, Carl Spengler's treatment with, 181-184  
 — vaccination, 200-201  
 Bovotuberculol, 59, 177  
  
 CALMETTE'S CL, 188-189  
 — tuberculin test, 58  
 Changes in toxin-sensitive cells, 13-16  
 Childhood, conjunctival test in, 66-67  
 —, cutaneous test in, 43-48  
 —, intracutaneous test in, 56  
 —, percutaneous test in, 51-53  
 —, subcutaneous test in, 88-90  
 —, tuberculin diagnosis in, 123-128  
 —, tuberculin treatment in, 269-274  
 Children, tuberculin diagnosis in, 123-128  
 Choice of tuberculin, 135-139  
 Cholin, 207  
 Complement-fixing antibodies, 14-16, 36  
 Conjunctival test, 58-69  
 — —, contra-indications to, 66-67  
 — —, control and significance, 61-64  
 — —, general verdict on, 68  
 — —, harm arising from, 64-66  
 — —, indications for, 67  
 — —, modification of, 68-69  
 — —, prognostic value of, 67-68  
 — —, technique of, 58-61  
 Contra-indications to cutaneous test, 43-44  
 — to conjunctival test, 66-67  
 — to percutaneous test, 52  
 — to subcutaneous test, 85-88  
 — to tuberculin treatment of pulmonary tuberculosis, 228-234  
 Control injections, diagnostic, 82



- Cumulative tuberculin action. *See* Hypersusceptibility
- Curative factors of tuberculin action, 24-36
- sera in tuberculosis, 208-217
- Cutaneous reaction, control and significance of, 40-43
- —, contra-indications to, 43-44
- —, Detre's differential, 48-49
- —, general verdict on, 48
- —, indications for, 44
- —, prognostic significance of, 46-47
- —, quantitative (Ellermann and Erlandsen), 47
- —, technique of, 38-40
- —, therapeutic significance of, 140, 141, 158
- —, v. Pirquet's, 48-49
- tests, 38-58
- tuberculin treatment, 144-145
- DENYS' tuberculin, 186-187
- Dermatology, tuberculin diagnosis in, 118-120
- — treatment in, 257-261
- Detre's modification of cutaneous test, 48-49
- Diagnosis, specific, of tuberculosis, 3-4, 37-123, 276-278
- Digestive organs, tuberculosis of, specific treatment of, 241-242
- — —, tuberculin diagnosis in, 109-110
- Dilution of tuberculin, 70-71
- Drop-bottle, v. Pirquet's, 39
- EAR, tuberculosis of, specific treatment of, 257
- —, tuberculin diagnosis in, 117-118
- Ellermann and Erlandsen's quantitative cutaneous test, 47
- Endotin, 187-188
- Escherich's needle-track reaction, 90-92
- Eye, tuberculosis of, specific diagnosis, 115-117
- —, specific treatment of, 250-257
- FEBRILE reaction, 80-81
- Fever, treatment of, 228-230
- Filtrase (Haentgens'), 195
- Focal Reaction, 27-28, 80, 83-84, 96-100
- GENERAL reaction, 82-83
- Genital tuberculosis, specific treatment of, 242-248
- —, tuberculin diagnosis of, 111-113
- Glandular tuberculosis, specific treatment of, 261-269
- —, tuberculin diagnosis of, 121-123
- HEYMAN'S protective inoculation, 202-203
- History of tuberculin, 132-135
- Hospitals and tuberculin, 5-9, 94, 95
- Hypersusceptibility in tuberculin treatment, 146, 150
- on repetition of a subcutaneous test, 75
- — of the conjunctival test, 60-61
- —, theories of, 19-22
- IMMUNE blood (IK), Carl Spengler's, in diagnosis, 70
- — — — — in treatment, 218-222
- Immunization against tuberculosis, active, 159-208
- — — on the lines of Jenner and Pasteur, 197-205
- — —, passive, 208-217
- Indications for the conjunctival test, 67
- — cutaneous test, 44
- — intracutaneous test, 56
- — percutaneous test, 51-52
- — subcutaneous test, 88
- — tuberculin treatment in general, 223-224
- — — — — in pulmonary tuberculosis, 225-228
- — various tuberculins, 135-139
- Injectio vacua, 82
- Intracutaneous test, 54-58
- — in animal experiments, 57-58
- — in veterinary medicine, 56-58
- Intrapulmonary tuberculin treatment, 142-143
- Intravenous tuberculin treatment, 142
- Iodized tuberculins, 193
- Iron tuberculin, for cutaneous test, 47-48
- — in treatment, 192



- JOINTS, tuberculosis of, specific treatment of, 265-269  
 — —, tuberculin diagnosis of, 121-123
- KLEBS' tuberculins, 177-178  
 Klimmer's protective inoculation, 203-204
- LANDMANN'S tuberculol, 175-177  
 Laryngeal tuberculosis, specific treatment of, 235-240  
 — —, tuberculin diagnosis of, 107-109  
 Lautier's tuberculin reaction, 53-54  
 Liguère's tuberculin reaction, 53  
 Lupus. *See* Skin, tuberculosis of
- MARAGLIANO'S serum, 209-210  
 Marmorek's serum, in diagnosis, 70  
 — —, in treatment, 211-214  
 — — (streptococcal), 216  
 Maximal dose, in tuberculin diagnosis, 76-78  
 — —, in treatment, 211-214  
 Meningitis, tubercular, diagnosis of, 113-114  
 — —, treatment of, 250  
 Mixed tuberculins, 185-186  
 Molliment, 194-195
- NASAL reactions, 69, 106  
 Nastin, 205-207  
 Needle-track reaction, 83  
 — — —, Escherich's, 90-92  
 Neurin, 207  
 New tuberculin (TR), 167-169  
 — — bacillary emulsion (BE), 169-173
- OLD tuberculin, in diagnosis, 38, 48, 50, 53, 54, 59, 69, 70  
 — — in treatment, 159-164  
 — —, sterilized injections of, 71-72  
 Ophthalmic reaction, 58-69  
 Opsonins (Wright's), 30-33  
 Original tuberculin, 163-164, 182
- PASSIVE immunization against tuberculosis, 208-217  
 Percutaneous tuberculin test, 49-54  
 — — —, contra-indications to, 52  
 — — —, control and significance of, 50-51  
 — — —, general verdict on, 52-53
- Percutaneous tuberculin test, indications for, 51  
 — — —, modifications of, 53-54  
 — — —, technique of, 50  
 — — treatment, 144-145  
 Peritoneal tuberculosis, specific treatment of, 249-250  
 — —, tuberculin diagnosis in, 114-115  
 Petruschky's serial treatment, 155-156  
 Phagocytosis, 33-35  
 Phytosoremid, 144  
 Phymatin, 59  
 Pleurisy, tubercular, specific treatment of, 249  
 — —, tuberculin diagnosis in, 114  
 Practice, general, and specific treatment, 9-11, 281-294  
 Pregnancy, specific treatment in, 234  
 —, tuberculin diagnosis in, 100  
 Principles of tuberculin treatment, 132-139  
 Prognostic value of tuberculin tests, 46-47, 53, 67-68, 105-106  
 Prosperol. *See* Molliment  
 Pseudo-reactions, 81-82  
 Psychogenous rises of temperature, 81-82  
 Puberty, tuberculin diagnosis in, 128  
 Pulmonary infusion, 142-143  
 — tuberculosis, specific treatment of, 224-234  
 — —, tuberculin diagnosis in, 93-106  
 — tuberculin reaction. *See* Tuberculin reaction.
- RECTAL administration of tuberculin, 144  
 — reaction, 69  
 Repetition of conjunctival test, 60-61  
 — of subcutaneous test, 75-76  
 Respiratory tract, diagnosis of tuberculosis of, 106-109  
 — —, specific treatment of tuberculosis of, 234-240  
 Rosenbach's tuberculin, 189-192
- SANATORIA and specific diagnosis, 3, 4, 95, 96, 277  
 — — treatment, 4-6, 283-284  
 Sanatorium treatment of tuberculosis, combined with tuberculin treatment, 132-133, 280-281, 284-286  
 — — —, value, 130-132, 280-286



- Scarifier, v. Pirquet's, 38  
 Selenin (Klebs'), 178  
 Sensitized bacillary emulsion, 173-175  
 Serial tuberculin treatment, 155-156  
 Serum treatment. *See* Passive immunization  
 Skin reaction. *See* Cutaneous reaction  
 —, tuberculosis of, specific treatment of, 257-261  
 — —, tuberculin diagnosis in, 118-120  
 Specific diagnosis of tuberculosis, 37-128, 276-278  
 — treatment, conclusions, 275-294  
 — —, general principles of, of tuberculosis, 132-139  
 — — of pulmonary tuberculosis, 224-234  
 — — of tuberculosis in childhood, 269-274  
 — — — in general, 4-11, 129-132  
 — — — of digestive organs, 241-242  
 — — — of ear, 257  
 — — — of eye, 250-257  
 — — — of glands, bones, and joints, 261-269  
 — — — of respiratory tract, 234-240  
 — — — of serous membranes, 249-250  
 — — — of skin, 257-261  
 — — — of urogenital organs, 242-248  
 — —, technique and methods of, of tuberculosis, 139-158  
 — tuberculin, 184-185  
 Spengler's, C., bovine tuberculin treatment, 181-184  
 — —, immune blood treatment (IK), 218-222  
 Stomachic application of tuberculin, 143  
 Streptococcus sera, 216-217  
 Subcutaneous test, 69-92  
 — —, administration of, 72  
 — —, contra-indications to, 85-88  
 — —, dosage in, for adults, 74-78  
 — — —, for children, 88-89  
 — —, indications for, 88  
 — — in veterinary medicine, 88  
 — — phenomenon of reaction in, 80-84  
 — —, preparation of dilutions for, 70-72  
 — — — used in, 69-70  
 — —, reaction in, 80  
 Subcutaneous test, technique of, 72-73  
 Suggestive rises of temperature, 81-82  
 TAURUMAN'S inoculation, 201  
 Tebean, 204-205  
 Tebesapin. *See* Molliment  
 Temperature control in tuberculin treatment, 147-148  
 Theories of the tuberculin reaction, 13-22  
 Tox-immunity, 24-27  
 Toxin-sensitive cells, changes in, during tuberculin reaction, 13-16  
 Toxin theory, 16-18  
 Tubercle immune blood (IK), 218-222  
 Tubercular serum, Hoechst, 214-216  
 Tuberculin action, curative factors of, 24-36  
 — — in animal experiments, 279-280  
 — cure in animal experiments, 279-280  
 — diagnosis, 2-4, 37-128, 276-278  
 — — in aural tuberculosis, 117-118  
 — — in children's diseases, 123-128  
 — — in general practice, 3, 95, 277  
 — — in ophthalmic tuberculosis, 115-117  
 — — in pulmonary tuberculosis, 93-106  
 — — in sanatoria, 4, 95-96, 277  
 — — in tuberculosis of digestive organs, 109-110  
 — — — of glands, bones and joints, 121-123  
 — — — of respiratory tract, 106-109  
 — — — of serous membranes, 113-115  
 — — — of skin, 118-120  
 — — in urogenital tuberculosis, 111-113  
 — dilutions, preparation of, 70-71  
 — —, ready for use, 71-72  
 —, harm caused by, after subcutaneous injection (Ulrici), 101-102, 278, 288  
 — — — in the conjunctival test, 64-66, 68  
 — inhalation, 143  
 — injections, intracutaneous, 50  
 — —, intravenous, 142  
 — —, subcutaneous, 72, 139-140  
 — reaction, phenomena of, 80-84  
 — —, theories of, 13-23  
 — —, treatment of, 145-150



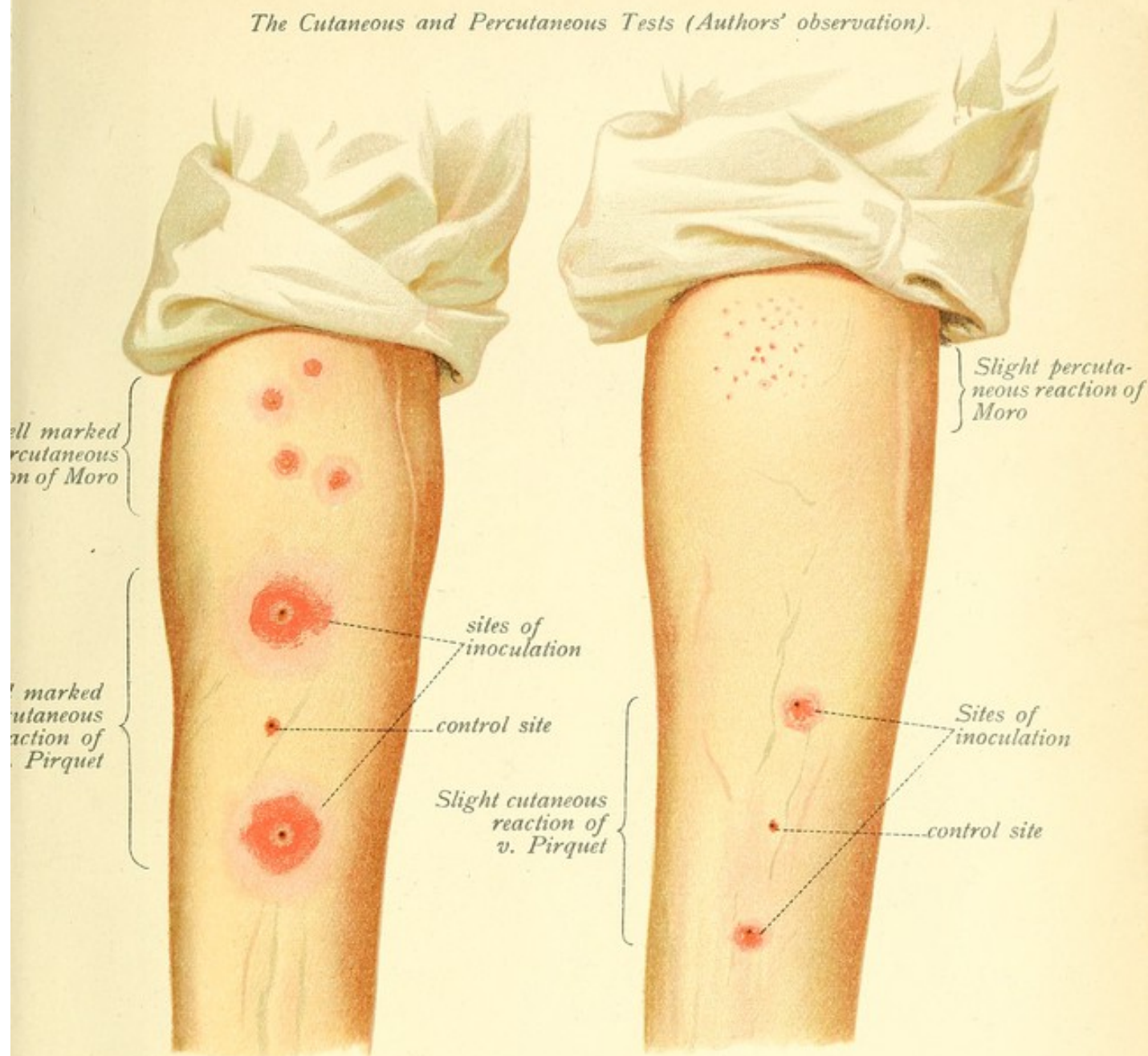
- Tuberculin test (Calmette's), 58
- —, conjunctival, 58-69
  - —, cutaneous, 38-49
  - —, Escherich's, 90-92
  - —, intracutaneous, 54-58
  - —, percutaneous, 49-54
  - —, subcutaneous, 69-80
  - treatment. *See also* Specific treatment
  - —, general principles of, 132-139
  - —, indications and contra-indications in pulmonary tuberculosis, 225-234
  - — in general, 129-132
  - —, other methods of application of, 142-145
  - —, technique and methods of, 139-158
  - vaseline for conjunctival test, 68-69
- Tuberculins for treatment, Béraneck's, 178-180
- — —, Klebs', 177-178
  - — —, Koch's, 159-164
  - — —, Landmann's, 175-177
  - — —, C. Spengler's, 181-184
  - — —, on the lines of Koch, 184-196
  - — — made from acid-fast bacilli, 197
  - — — made from bird-, slow-worm-, fish tubercle bacilli, 197-199
- Tuberculins for treatment, sensitized, 173-175
- Tuberculinum purum, 187-188
- Tuberculocidin (Klebs'), 177
- Tuberculol (Landmann's), 175-177
- Tuberculomucin, 196
- Tuberculonastin, 206
- Tuberculoplasmin, 195-196
- Tuberculoprotein, 178
- Tuberculosis diagnosticum (Hoechst), 59
- Tuberculosozin, 178
- URETHRAL reaction, 69
- Urinary organs, specific treatment of tuberculosis of, 242-248
- —, tuberculin diagnosis in tuberculosis of, 111-113
- Urogenital tuberculosis, specific treatment of, 242-248
- —, tuberculin diagnosis in, 111-113
- VACCINE treatment, 218
- Vacuum tuberculin, 182
- Vaginal reaction, 69
- Veterinary medicine and tuberculin tests, 48, 56-57, 59, 63, 64, 69, 88
- WRIGHT's opsonins, 30-33



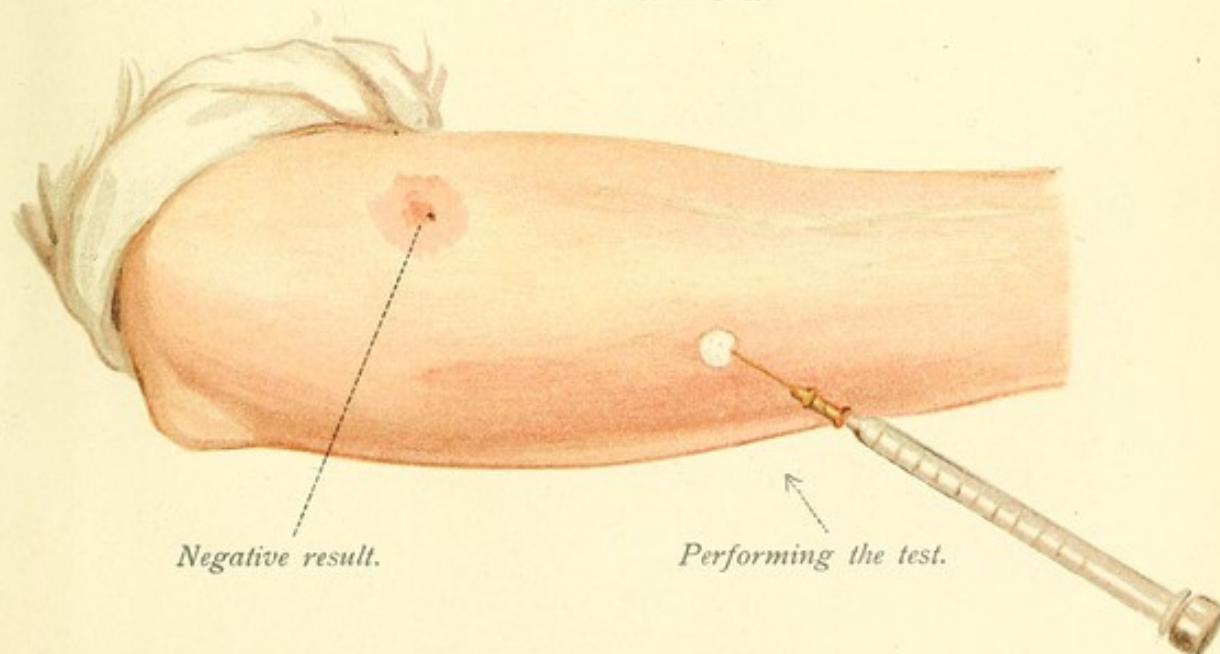




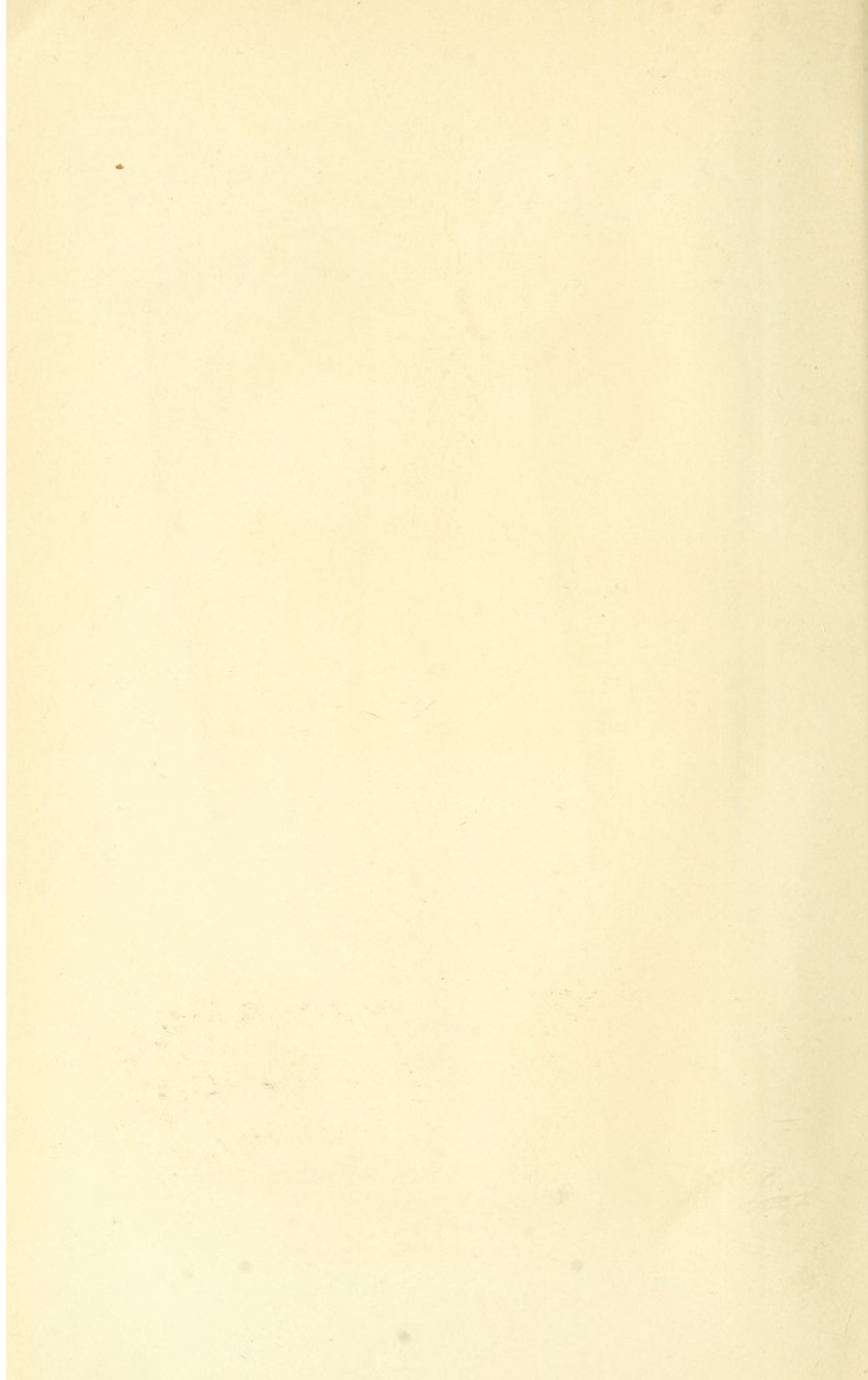
*The Cutaneous and Percutaneous Tests (Authors' observation).*



*The Intracutaneous Test.*

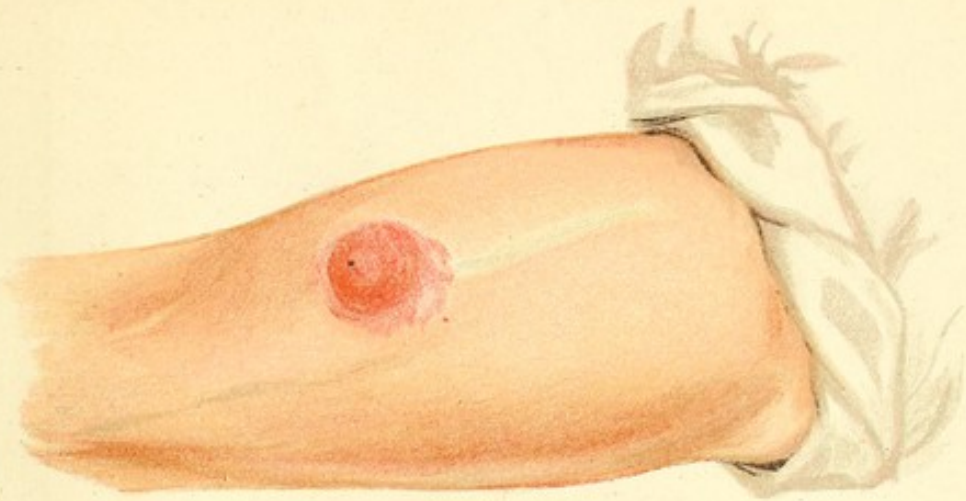




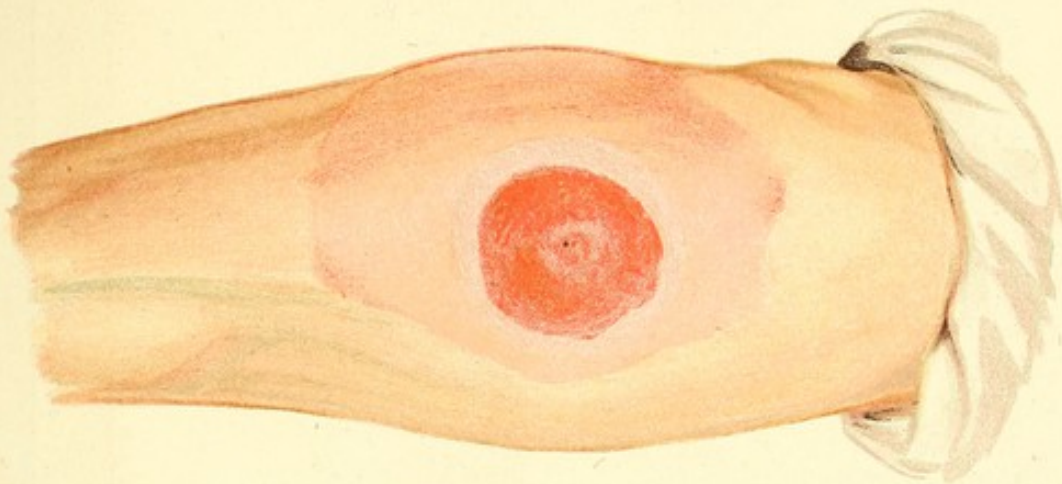




*Intracutaneous Test (Authors' observation).*

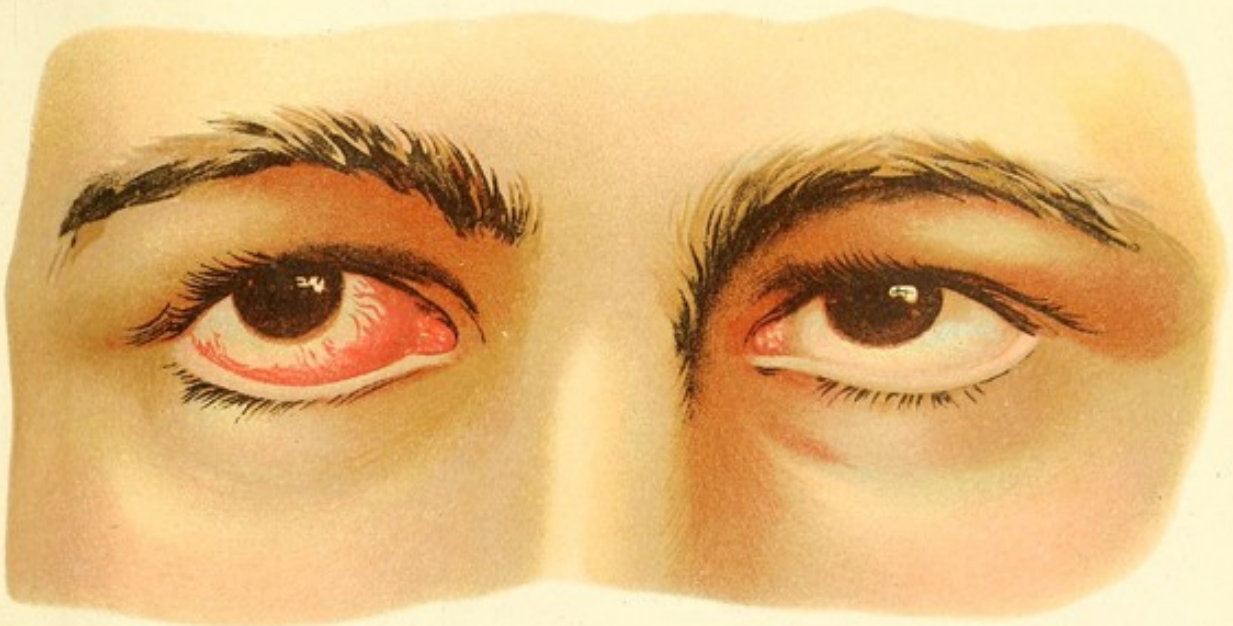


*Slight reaction.*



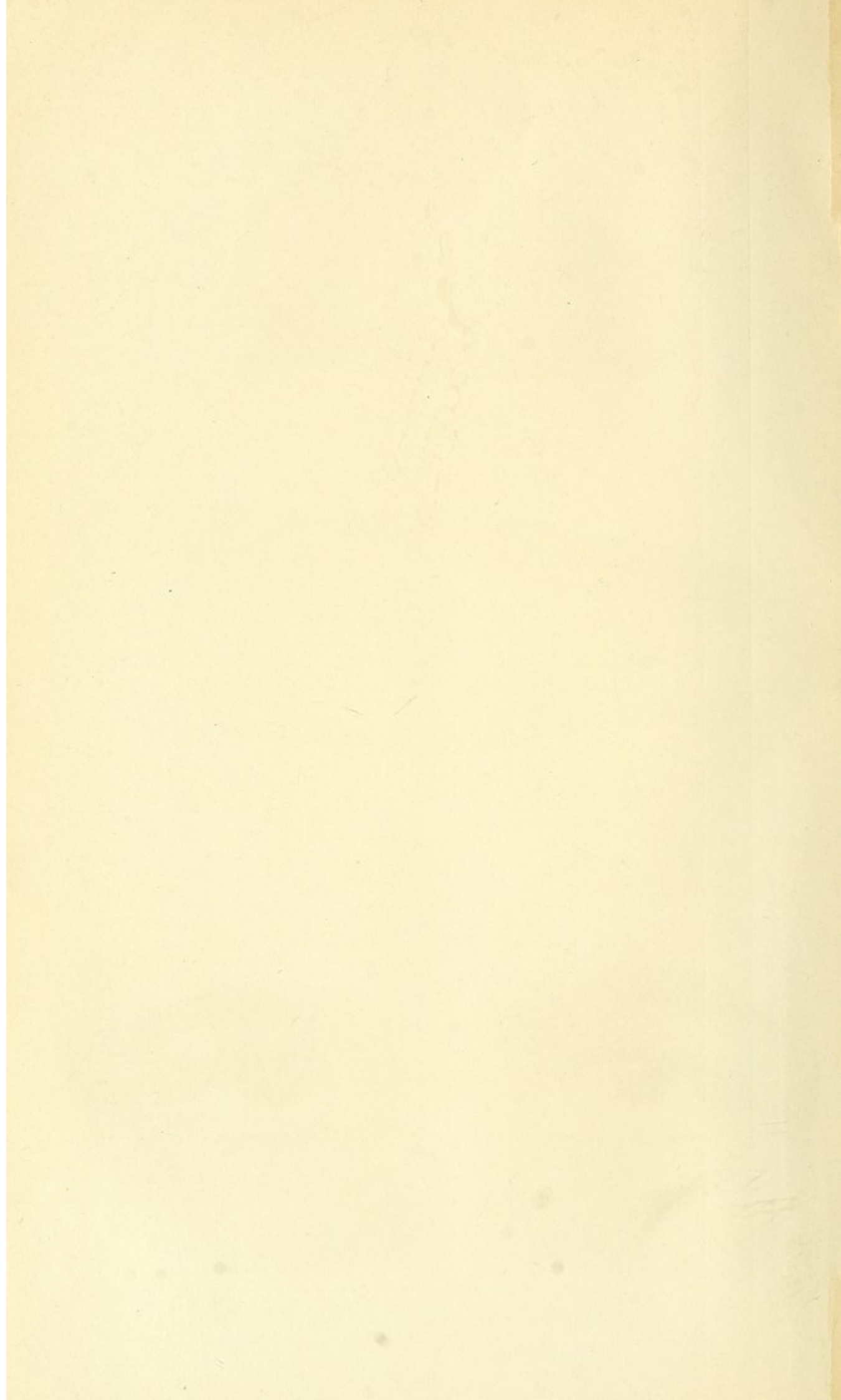
*Well marked reaction.*

*Conjunctival Test (Authors' observation).*

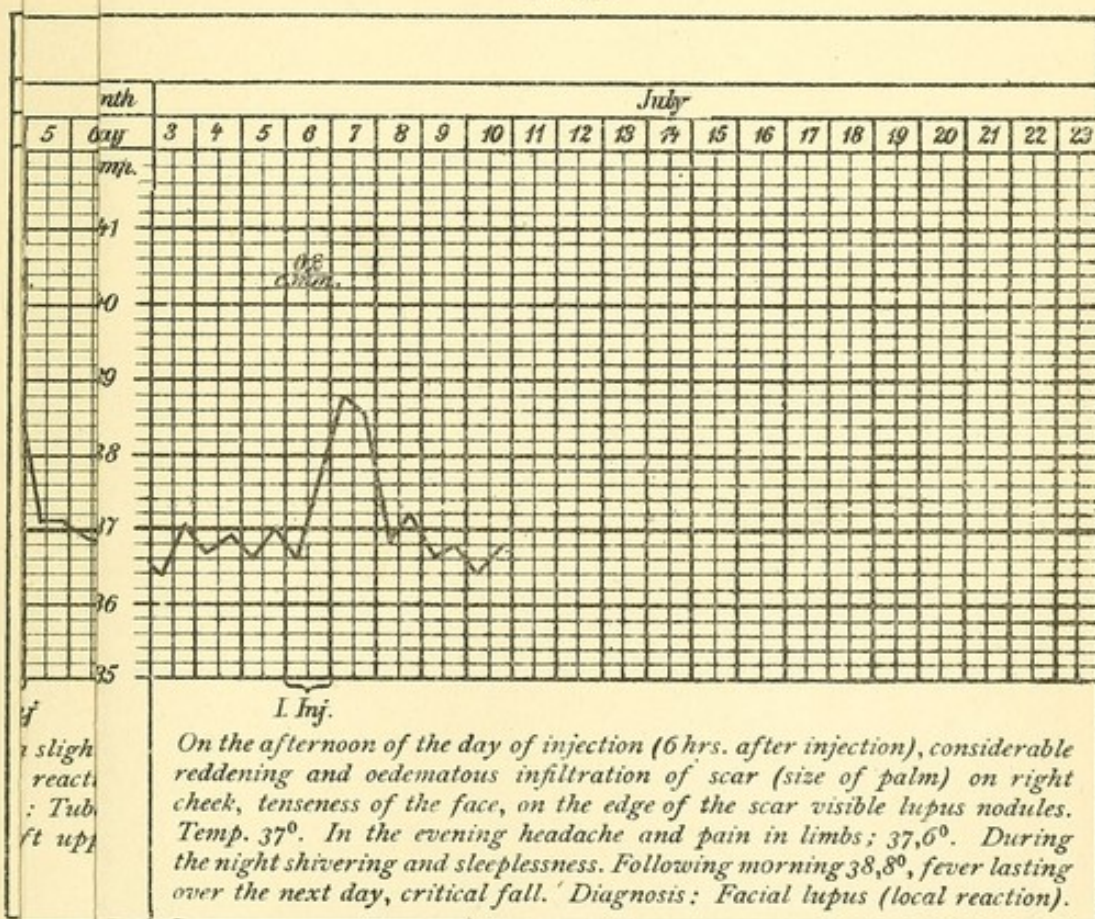
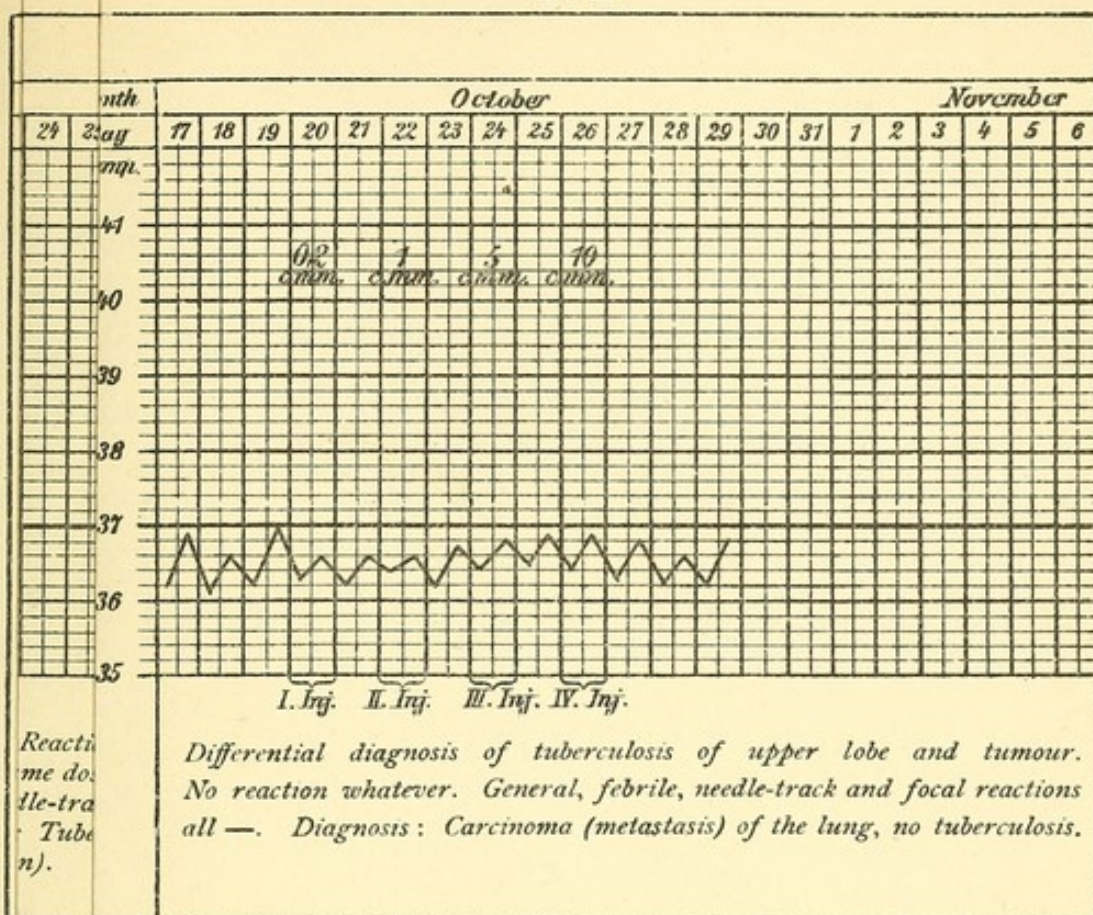


*Moderate Conjunctival Reaction of the right eye.*

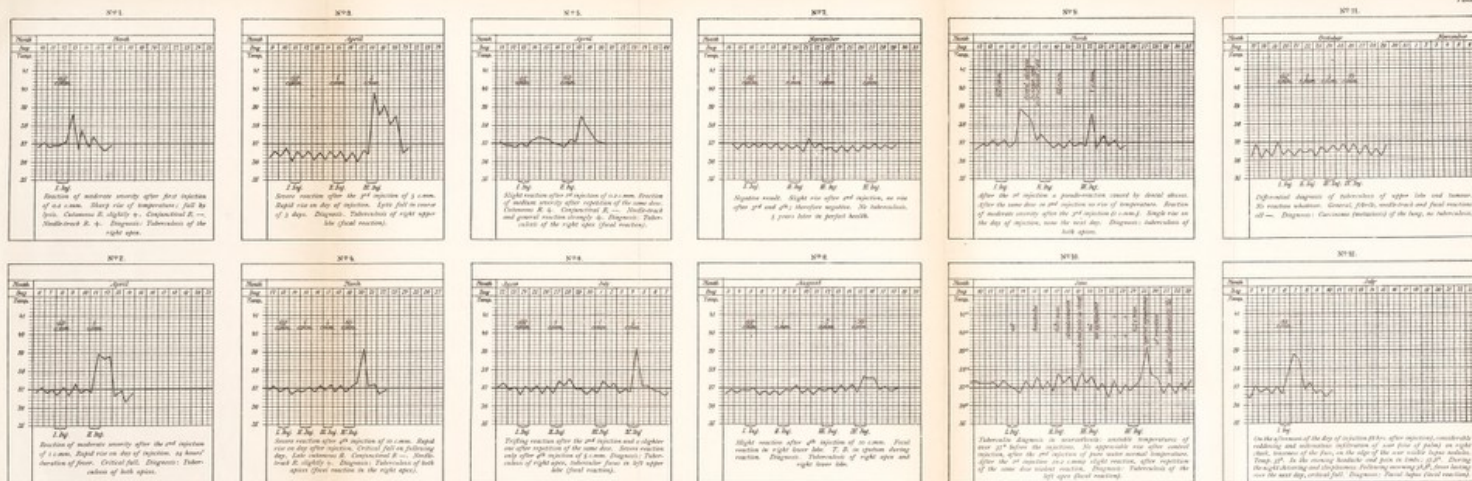






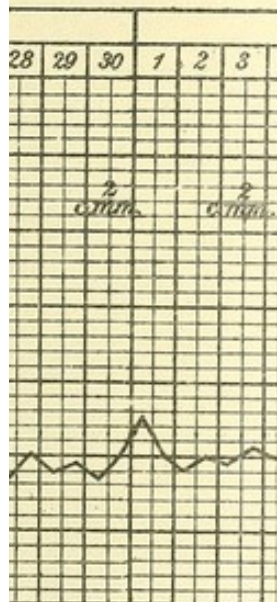
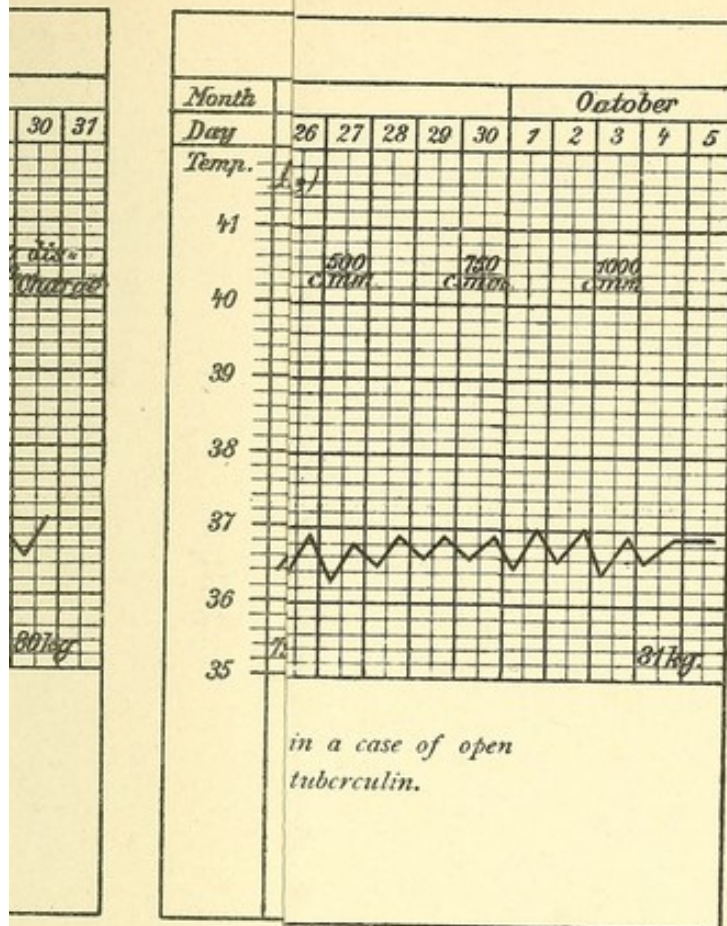






#### DIAGNOSTIC INJECTIONS.

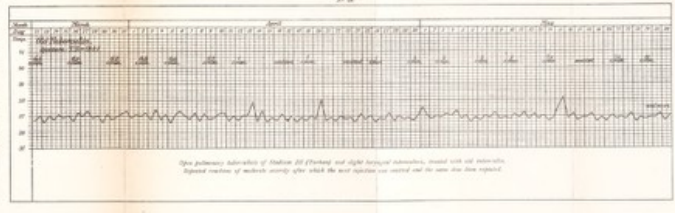
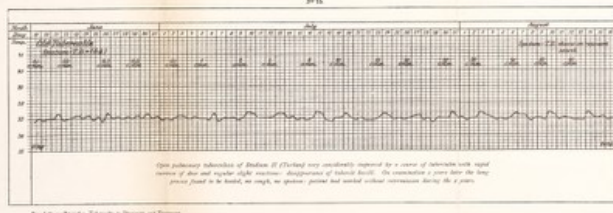
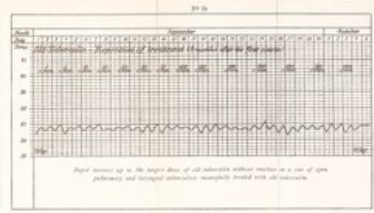
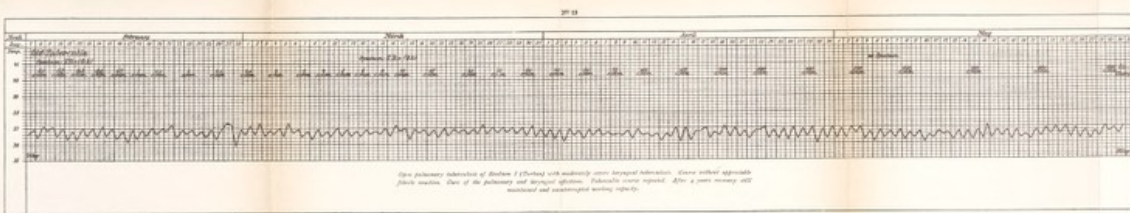




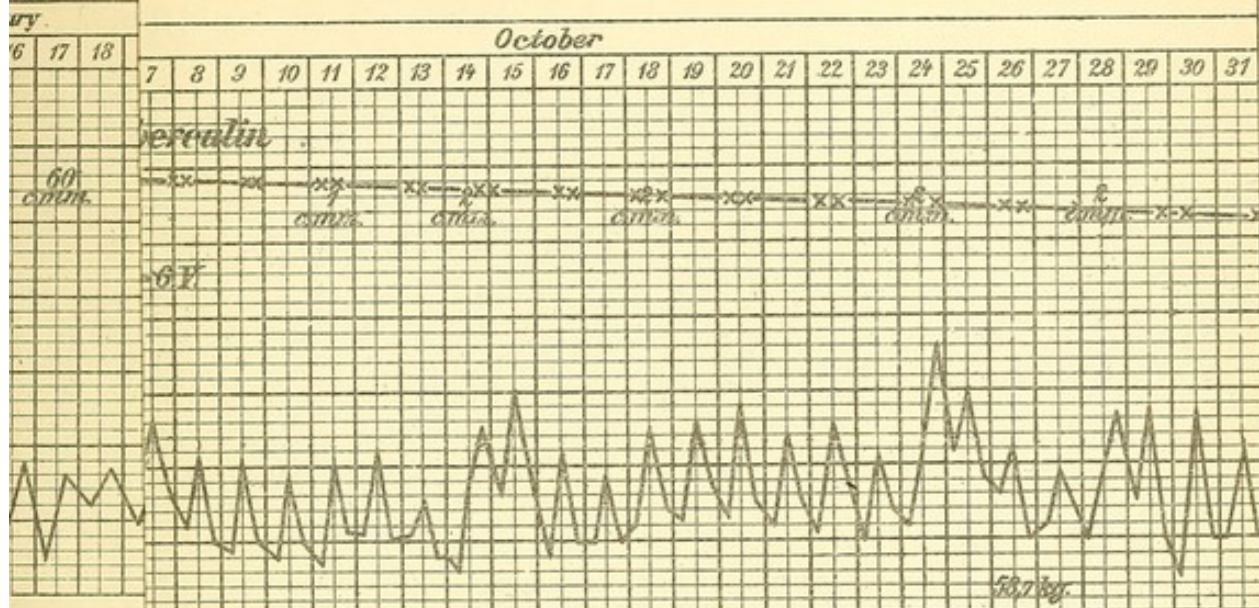
tuberculosis, treated and the same



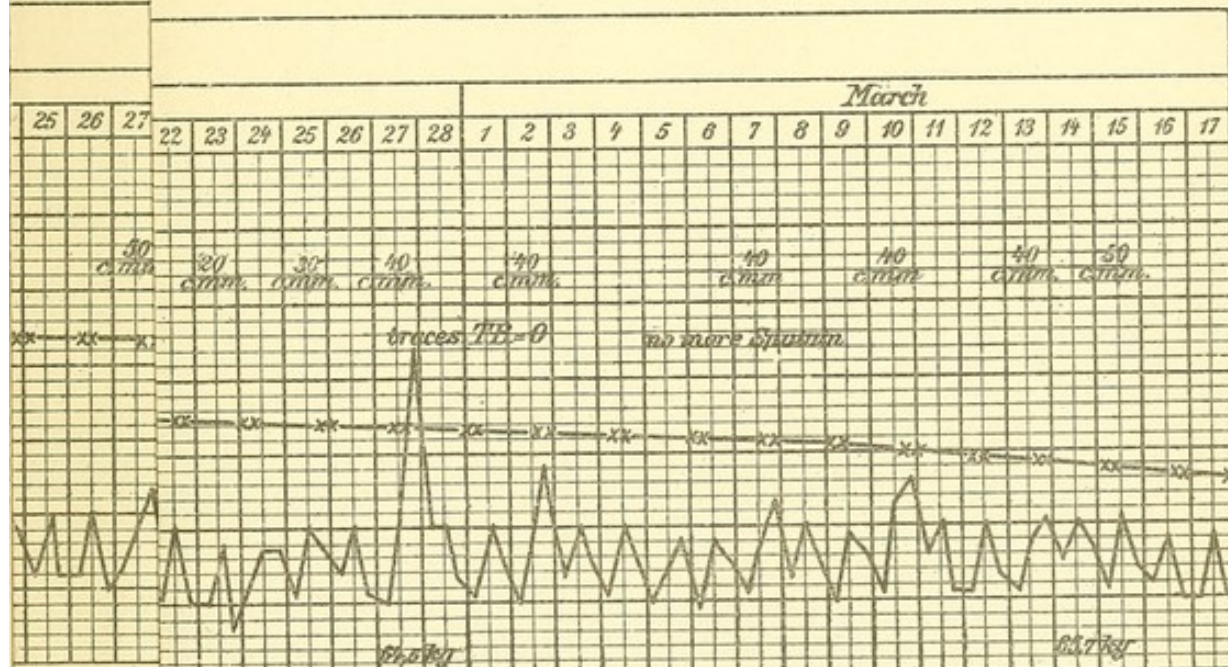






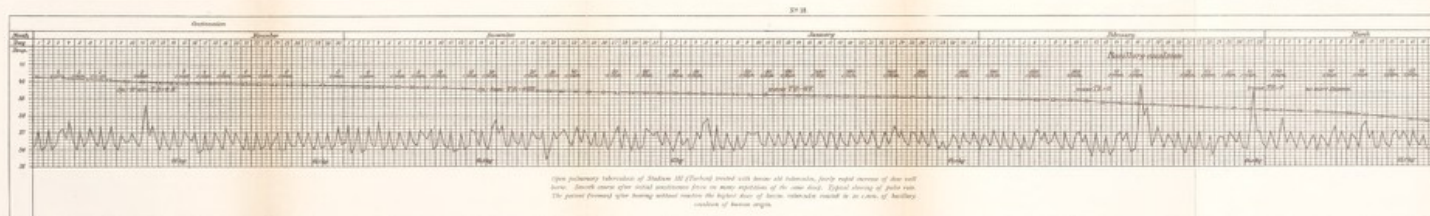
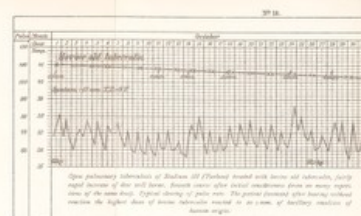
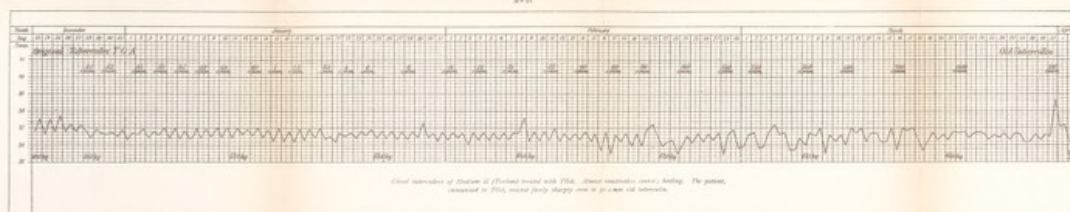


tuberculosis of Stadium III (Turban) treated with bovine old tuberculin, fairly reactionless. Smooth course after initial sensitiveness (even on many repetitions of 0.5 c.mm. old dose). Typical slowing of pulse rate. The patient (woman) after bearing without the best doses of bovine tuberculin reacted to 20 c.mm. of bacillary emulsion of human origin.



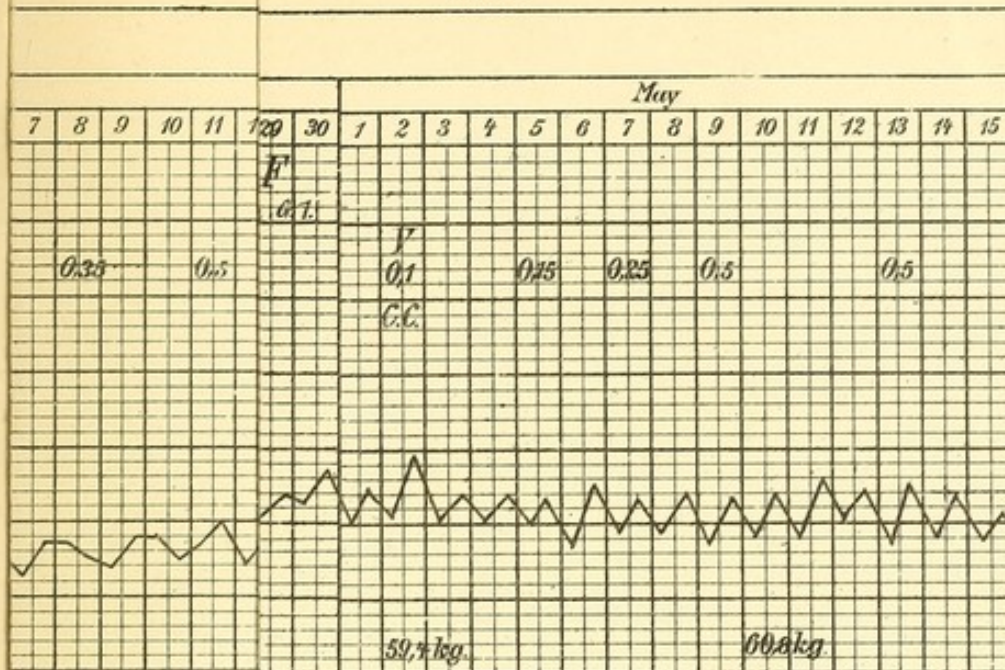
mary tuberc  
oth course o  
(woman) a



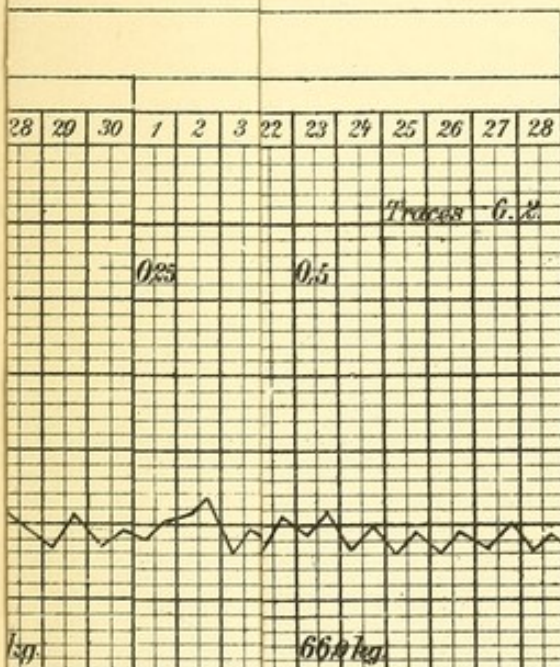




Nº 20.

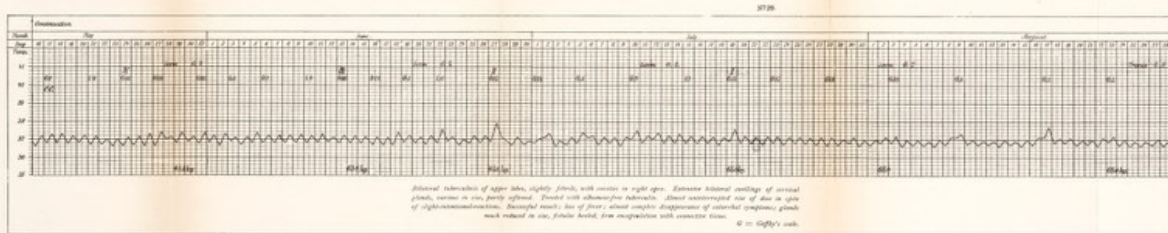
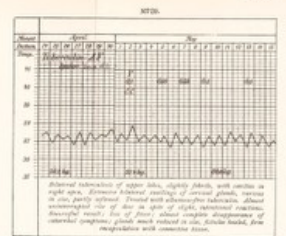
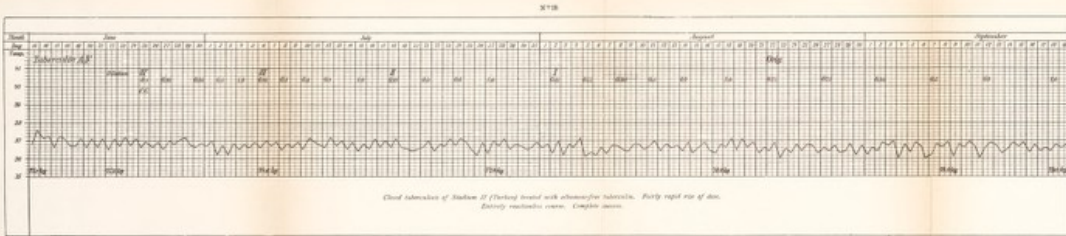


tuberculosis of upper lobes, slightly febrile, with cavities in extensive bilateral swellings of cervical glands, various softened. Treated with albumose-free tuberculin. Almost success. Fairly rise of dose in spite of slight, intentional reactions. Alt; loss of fever; almost complete disappearance of toms; glands much reduced in size, fistulae healed, firm encapsulation with connective tissue.

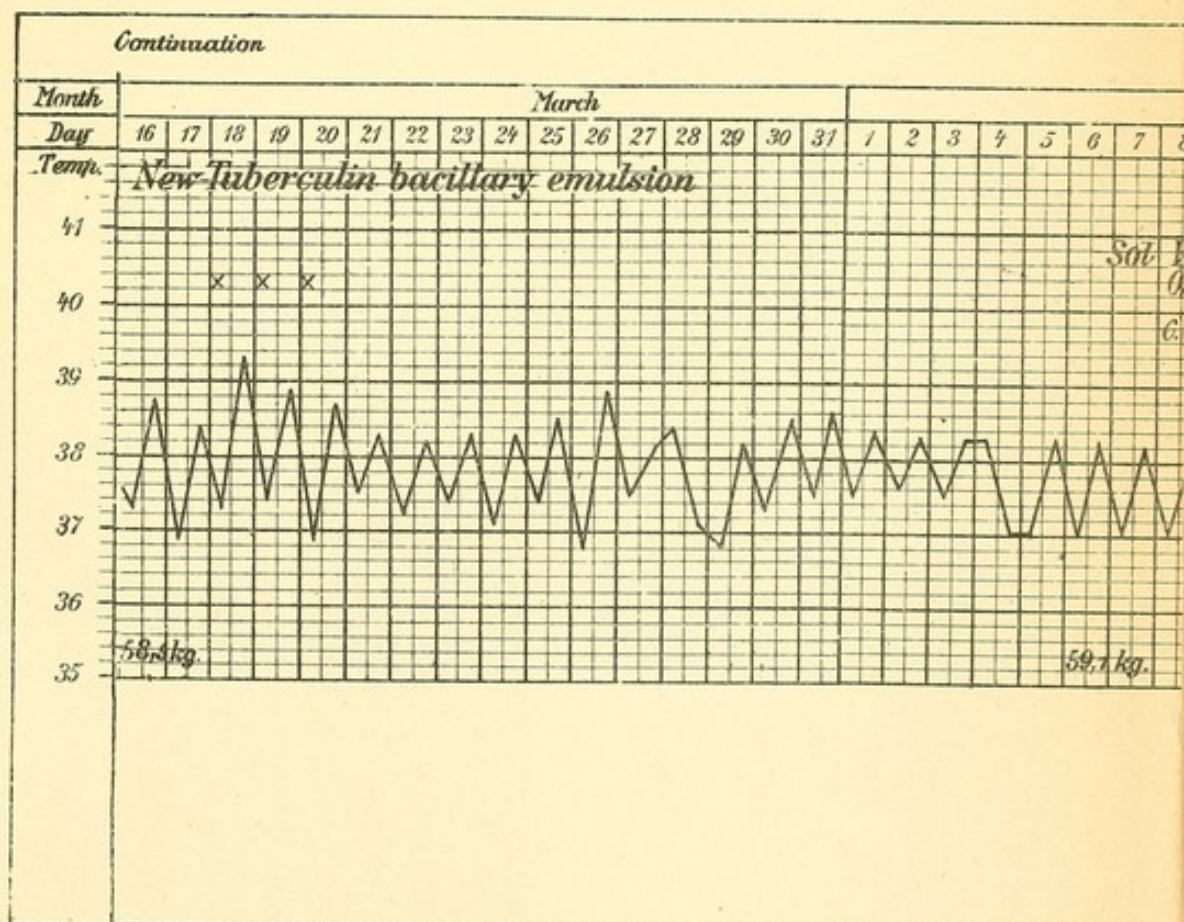
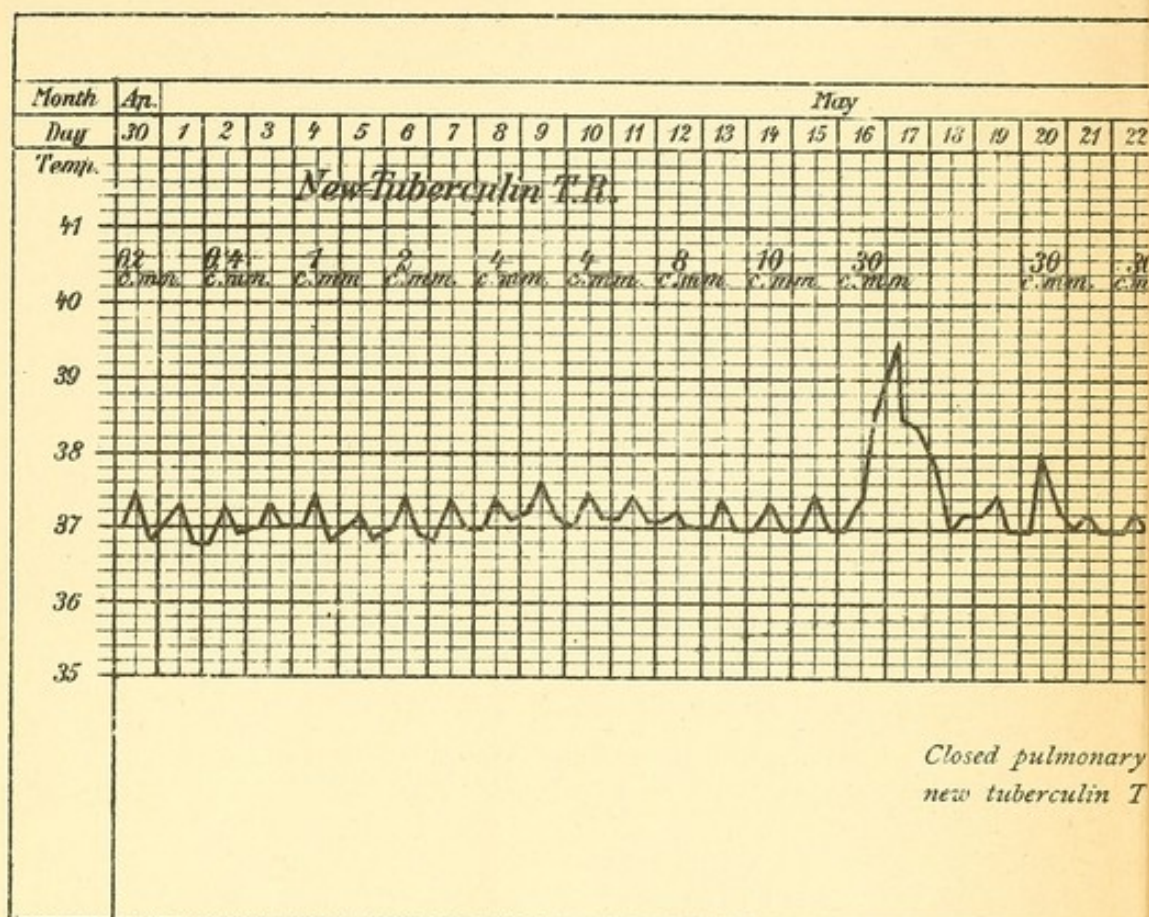


er lobes, slightly fe  
y softened. Treated  
Successful result;  
reduced in size, fist

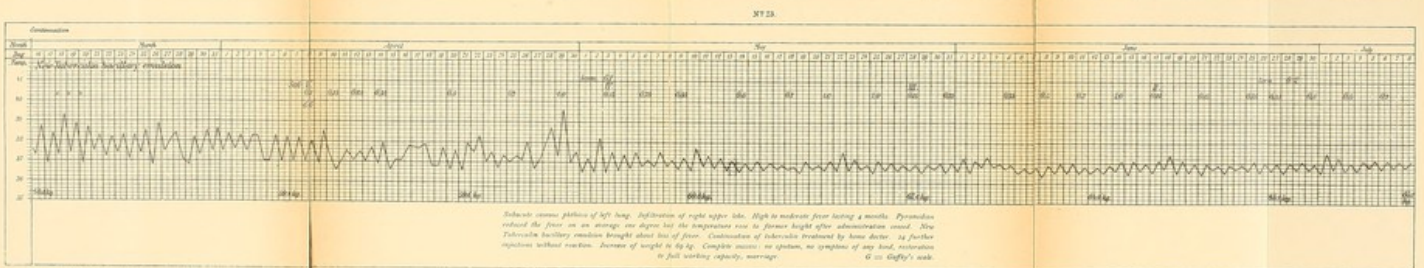
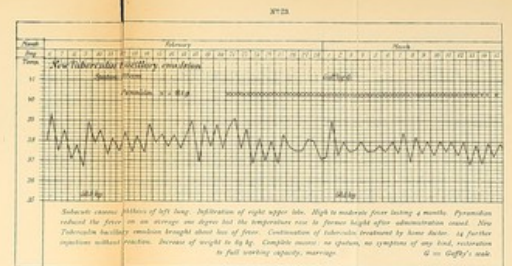
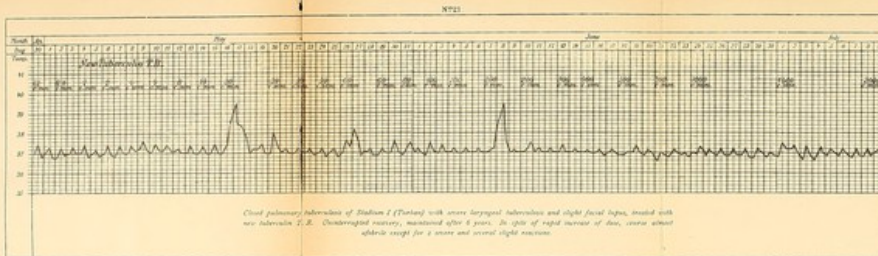




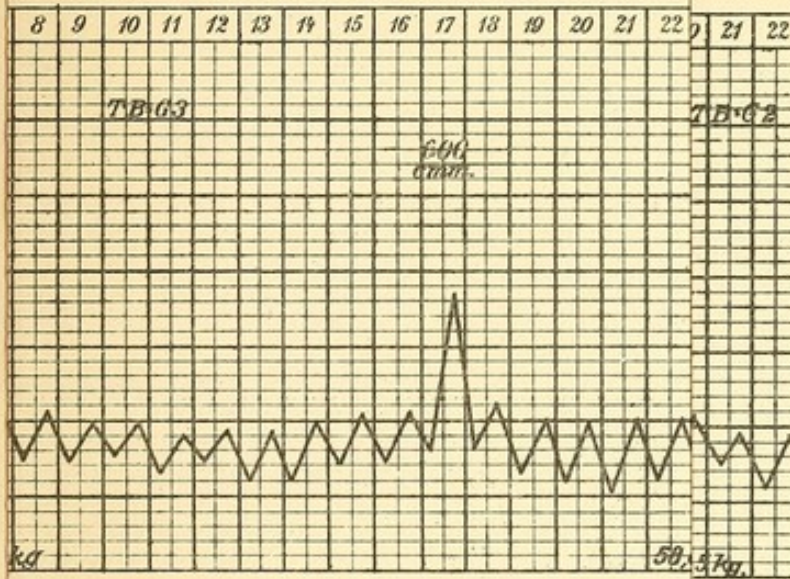




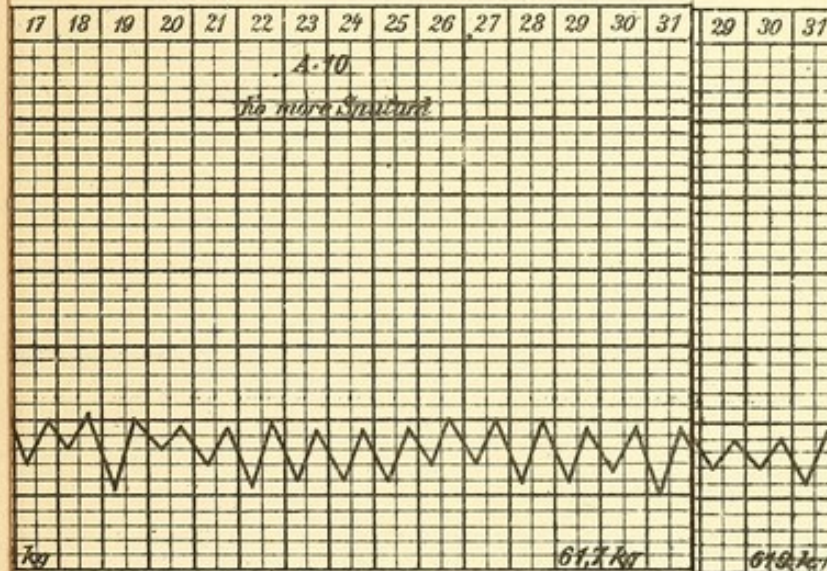






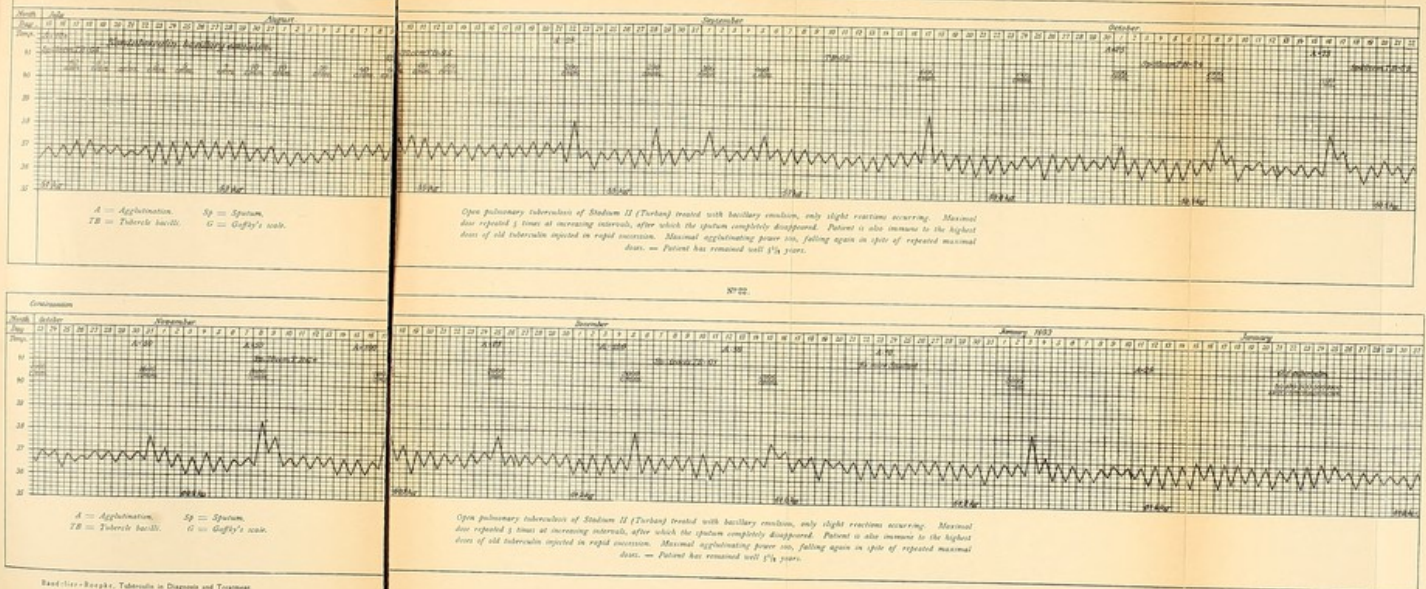


n, only slight reactions occurring. Maximal  
peared. Patient is also immune to the highest  
o, falling again in spite of repeated maximal  
ars.

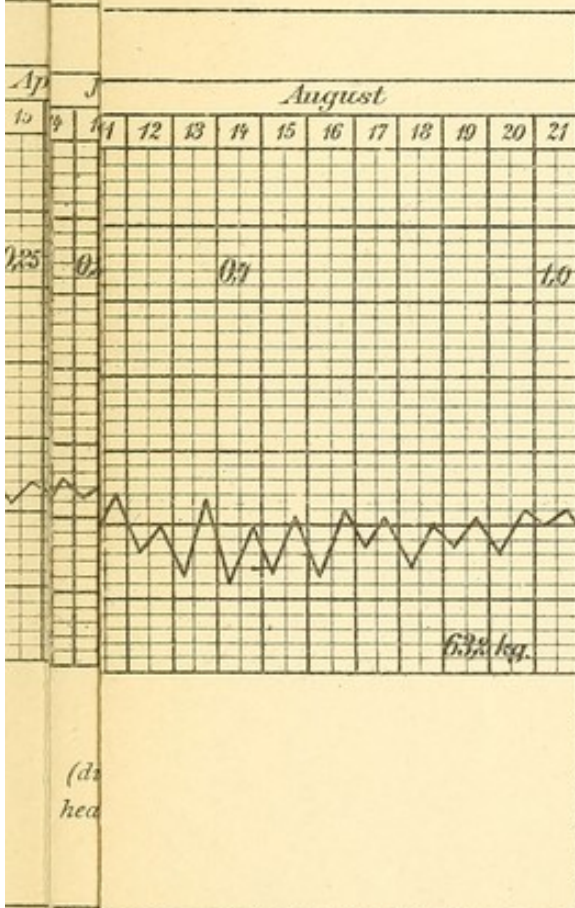
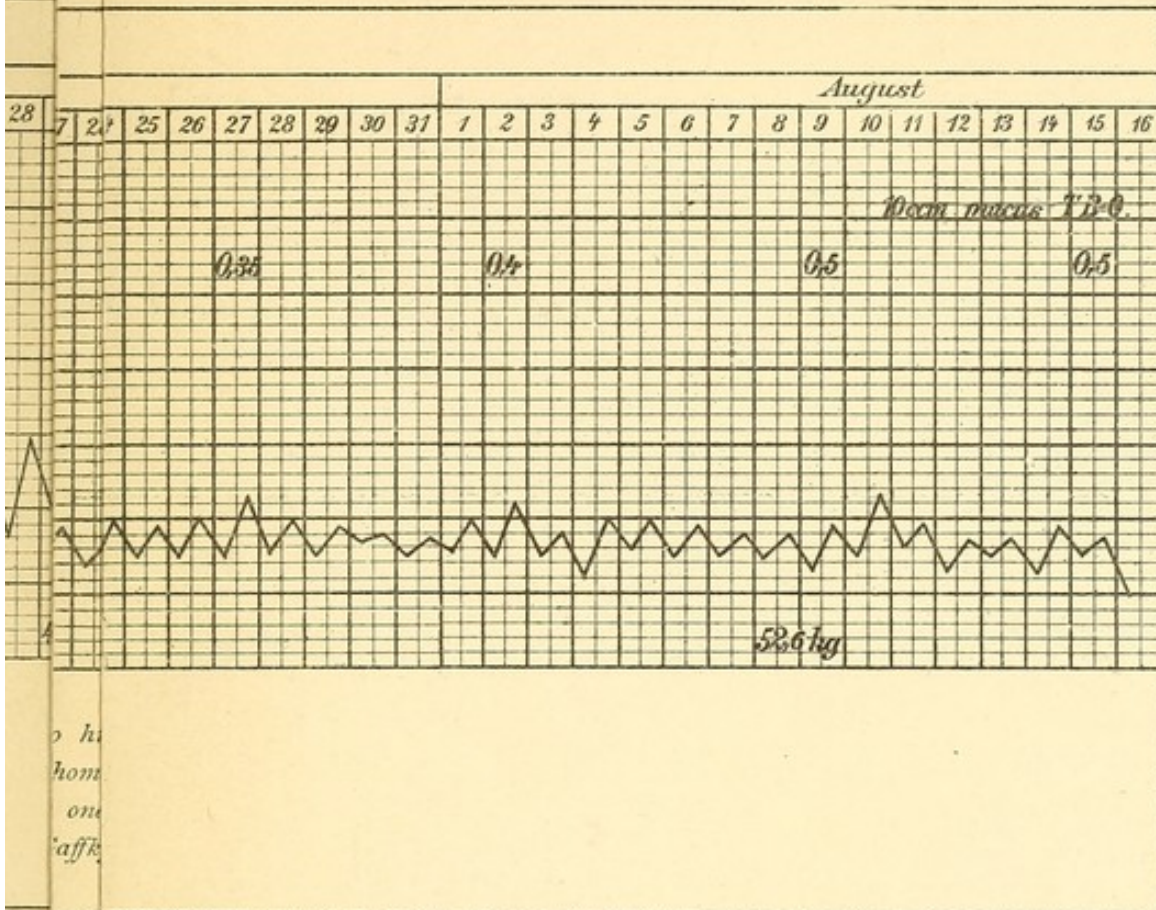


n, only slight reactions occurring. Maximal  
peared. Patient is also immune to the highest  
o, falling again in spite of repeated maximal  
ars.

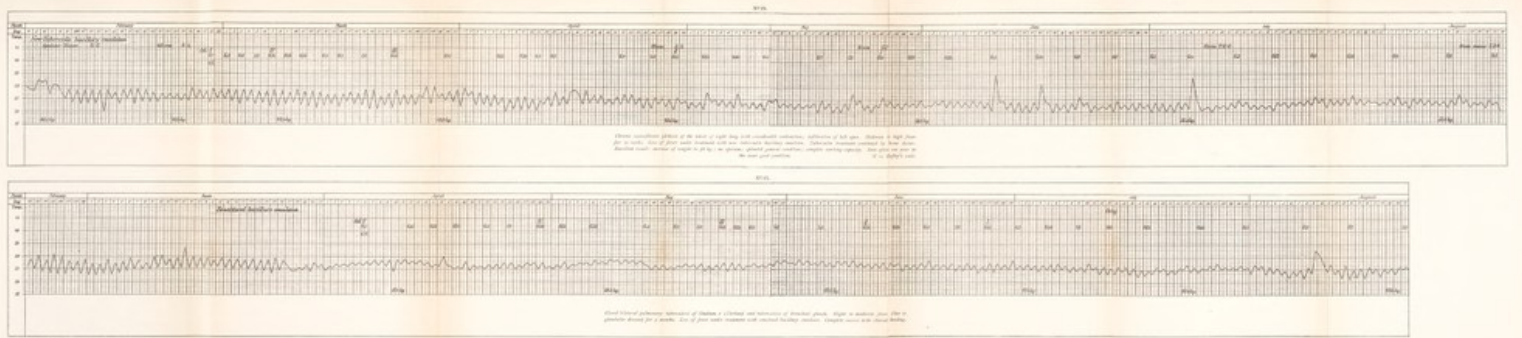




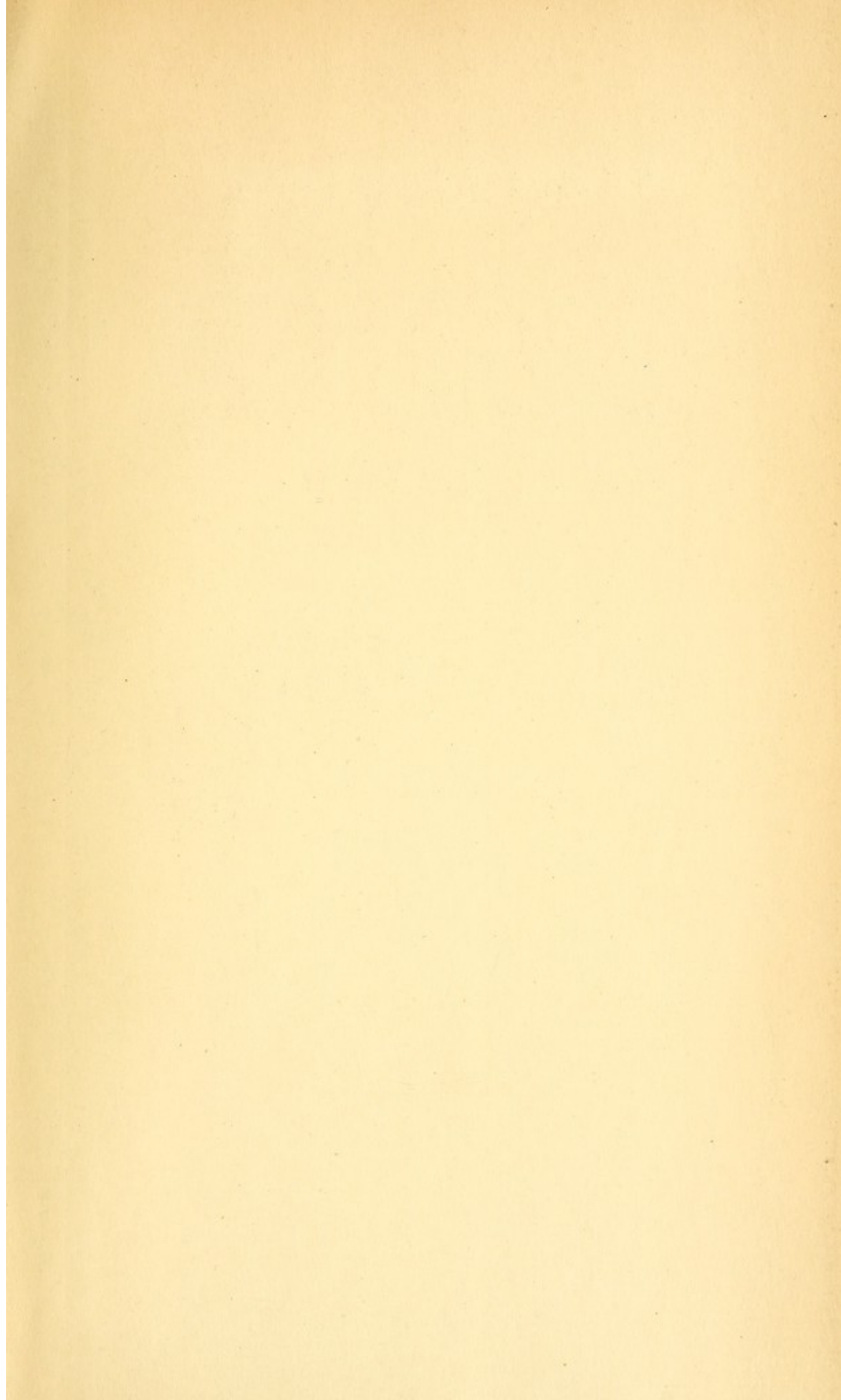














Date Due

11-1-32

NOV 18 '32





RC 311 20

B223

Bandelier and Roepke  
Tuberculin

Maloney

9 cadaver

1000000

1000000

1000000

1000000

1000000

1000000

1000000

1000000

1000000

1000000



