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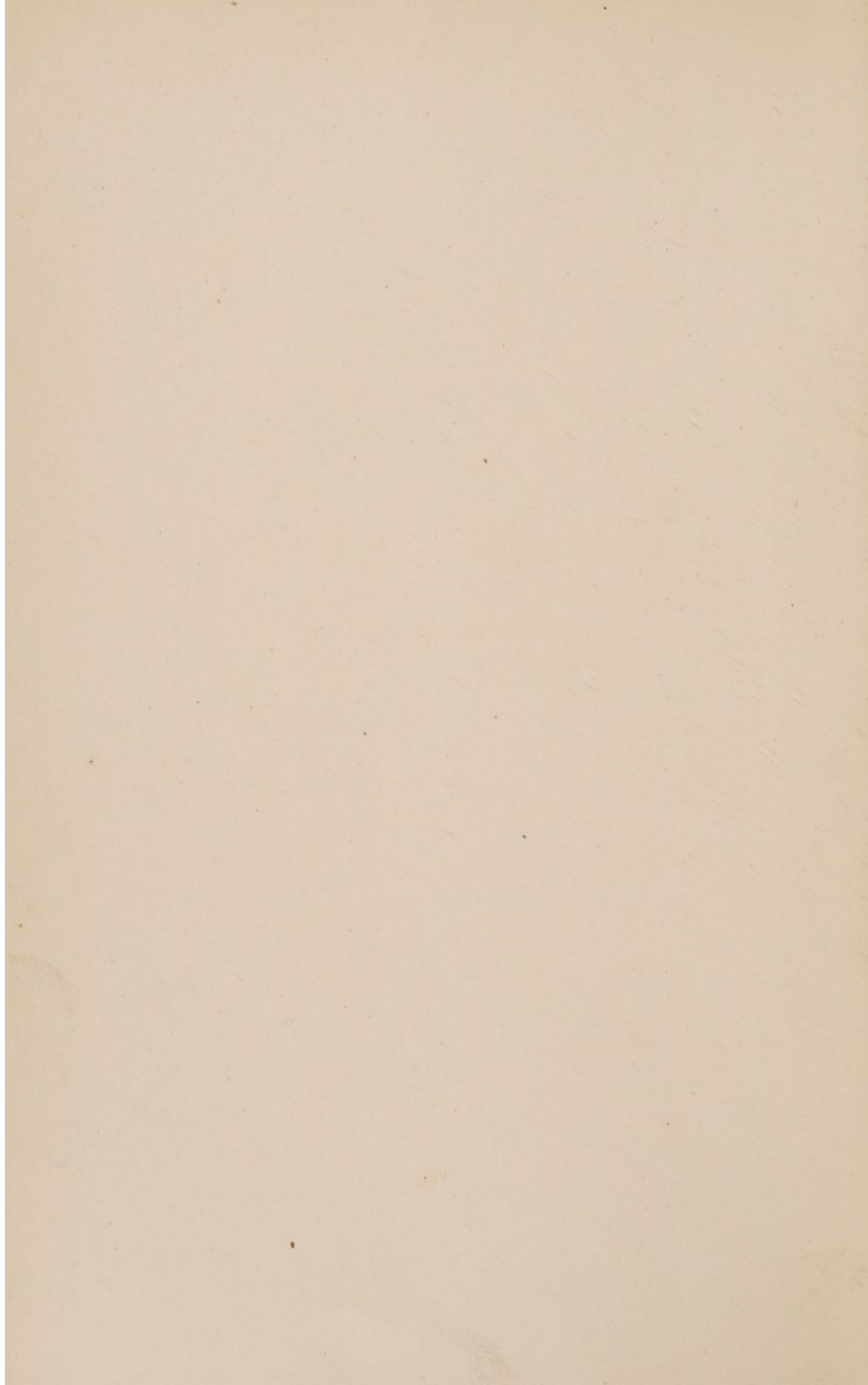


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TUBERCULIN
IN DIAGNOSIS
AND TREATMENT



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TUBERCULIN

IN DIAGNOSIS AND TREATMENT

BY

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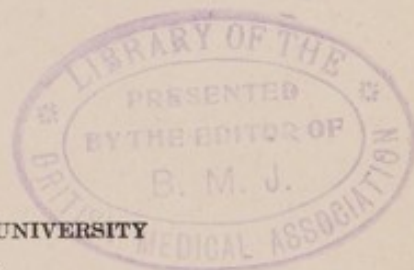
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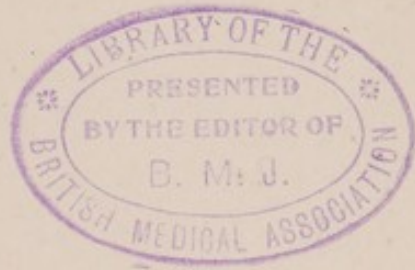


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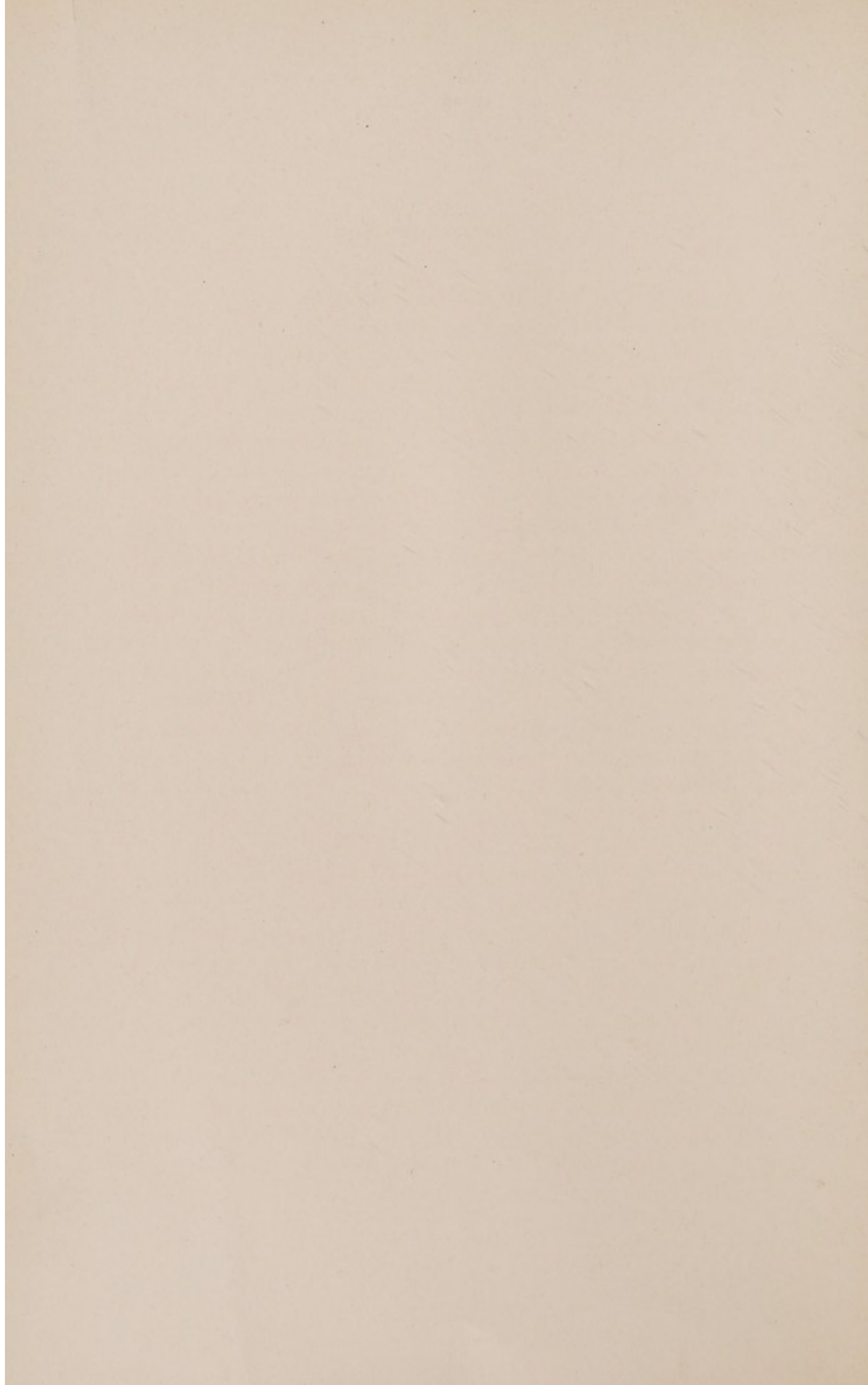
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TO
HENRY PHIPPS
AS A MARK OF OUR AFFECTION
AND GRATITUDE





PREFACE

The use of tuberculin in diagnosis and treatment has received wide attention during the past ten years. New methods of application in diagnosis have stimulated a keen interest to determine their value, and recent changes in attitude toward important questions bearing upon immunity have provoked extensive researches, undertaken to make clear its mode of action. Tuberculin treatment, sternly rejected after its unsuccessful introduction, has again become widely popular and discussion is waged as to its true value, the most desirable preparation and the best methods of administration. A voluminous literature has grown up, and from these innumerable contributions we are now in a position to filter off certain facts that have crystallized. About much we are still uncertain, but there is enough that is definite to permit us to take bearings for our practical course. While this literature is easily accessible, it is widely distributed and a large part of the best of it is in foreign languages. No satisfactory summary has appeared in English, and such a summary seems particularly desirable, as overstatements and misconceptions incident to early enthusiasm have stuck fast in the minds of many and have remained uncorrected by the overwhelming evidence of later investigations. In our experience there is a very general lack of knowledge of precisely what a reaction to tuberculin means, and of what account is the information gained from its use when applied to a particular instance. Numerous cases are still sent to us with a diagnosis of pulmonary tuberculosis based solely upon a positive cutaneous reaction, and in medical discussion one hears the most bizarre interpretations of the subcutaneous test.

During the past five years we have used tuberculin largely, both in diagnosis and treatment, at the Phipps Dispensary of the Johns Hopkins Hospital, and the experience we have gained is made the basis of this presentation. It is to be expected that we have come

PREFACE

to conclusions which do not in all points agree with those reached by others, and it is only natural that we should emphasize our own attitude. This we do not hesitate to do, but shall earnestly strive as well to present fairly our difference and add such pertinent evidence as may allow the reader to form his own opinion. Nothing is further from our aim than to give a complete critical review of the whole literature on tuberculin. Our work has forced us to familiarize ourselves with the most important contributions and from these we shall freely draw. Our purpose is to produce a book that may serve as a guide to those interested but inexperienced in the use of tuberculin and a source where reliable, if not exhaustive, information on the subject may be sought. It is, therefore, intended primarily for physicians interested in medicine generally and for students, rather than for tuberculosis specialists, although we hope it may not wholly lack interest even for these. We further hope that the book may prove to be a means of establishing a more precise and consistent attitude than now exists in the profession toward tuberculin diagnosis and treatment.

Before speaking of the practical application of tuberculin to diagnosis and treatment we shall consider the general principles that underlie its action. Unfortunately these are far from clear, and in spite of the vast amount of research directed toward their elucidation but little actual advance has been made. The work has, however, resulted in the suggestion of many interesting and fruitful points of view which have stimulated investigation to follow new paths and promise ultimate solution. It is important that we should be familiar with the general truths known about tuberculin before undertaking to use it, and highly desirable that we should have some acquaintance with the observations upon which these truths rest. The application of tuberculin to treatment necessitates also an inquiry into what is known concerning processes leading to spontaneous recovery and what part tuberculin may play in assisting or instituting such processes. We deem it advisable to consider these questions at once, and, if we succeed in making them clear, the way will be opened to a ready appreciation of the significance of methods and deductions in practical application.

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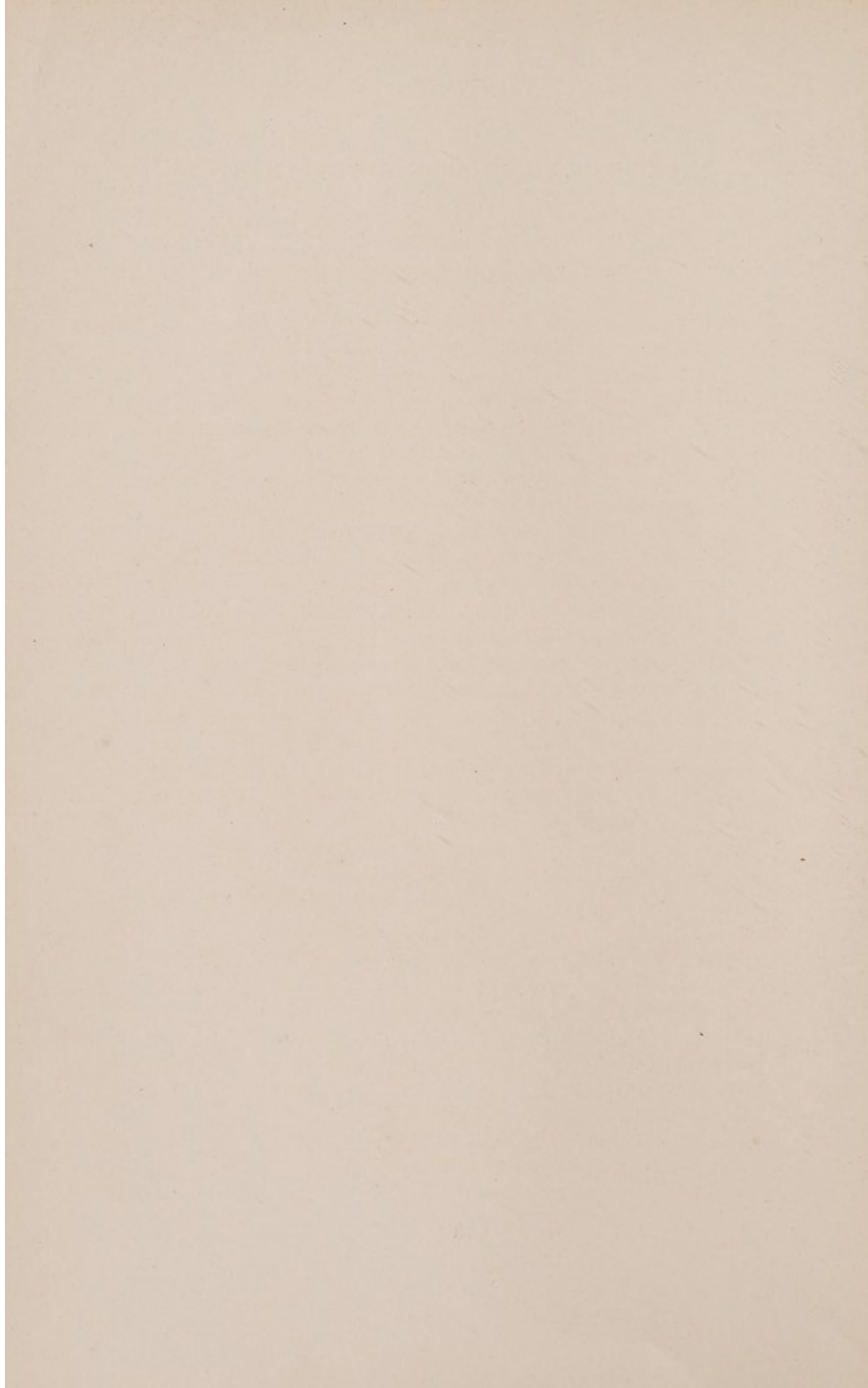
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TUBERCULIN

I

THE SCIENTIFIC PRINCIPLES UNDERLYING THE DIAGNOSTIC AND THERAPEUTIC USE OF TUBERCULIN

THE TUBERCULIN REACTION

Of all the phenomena medical investigation has called forth there is none that has attracted wider interest than the group of symptoms that follows the injection of tuberculin into tuberculous animals, spoken of as the tuberculin reaction. Koch was the first to note this remarkable relation and it is instructive to refer to his original description and explanation and compare with it the changes in attitude that twenty years of constant application have brought about. In these early experiments Koch used a tuberculin made by reducing on the water bath a six-to-eight-weeks-old glycerin bouillon culture of tubercle bacilli to one-tenth its volume and filtering. The filtrate is a dark brown, rather viscid, liquid of fragrant odor which has subsequently become designated as O. T., or original tuberculin. He tells¹ in a very graphic way how he came to hit upon the use of tuberculin in treatment. "When one vaccinates a healthy guinea pig with a pure culture of tubercle bacilli the wound as a rule closes and in the first few days seems to heal. However, in from ten to fourteen days a hard nodule appears which soon breaks down, leaving an ulcer that persists to the time of death of the animal. There is

¹ Koch: Fortsetzung der Mittheilungen über ein Heilmittel gegen Tuberkulose. Deutsch. med. Wehnschr., 1891, xvii, 101.

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quite a different sequence of events when a tuberculous guinea pig is vaccinated. For this experiment animals are best suited that have been successfully infected four to six weeks previously. In such an animal the inoculation wound likewise promptly unites. However, no nodule forms, but on the next or second day after a peculiar change occurs. The point of inoculation and the tissues about, over an area of from 0.1 to 1. cm. in diameter, grow hard and take on a dark discoloration. Observation on subsequent days makes it more and more apparent that the altered skin is necrotic. It is finally cast off and a shallow ulceration remains which usually heals quickly and permanently without the neighboring lymph glands becoming infected. Inoculated tubercle bacilli act very differently then upon the skin of healthy and tuberculous guinea pigs. This striking action is not restricted to living tubercle bacilli but is equally manifested by dead bacilli, whether they be killed by exposure to low temperature for a long time or to the boiling temperature, or by the action of various chemicals.

“After having discovered these remarkable facts, I followed them up in all directions and was further able to show that killed pure cultures of tubercle bacilli ground up and suspended in water can be injected in large amounts under the skin of healthy guinea pigs without producing any effect other than local suppuration. Tuberculous guinea pigs, on the other hand, are killed, in from 6 to 48 hours according to the size of the dose given, by the injection of small quantities of such a suspension. A dose which just falls short of the amount necessary to kill the animal may produce extensive necrosis of the skin about the point of injection. If the suspension be diluted until it is just visibly cloudy, the injected animals remain alive, and if the administration is continued with one-to-two-day intervals a rapid improvement in their condition takes place; the ulcerating inoculation wound becomes smaller and is finally

THE TUBERCULIN REACTION

replaced by a scar, a process that never occurs without such treatment; the swollen lymph glands become smaller; the nutrition improves; and the disease process, unless it be too far advanced and the animal dies of exhaustion, comes to a standstill.

“Thus was established the basis for a rational treatment of tuberculosis. However, such suspensions of killed tubercle bacilli are unsuitable for practical use, since they are neither absorbed nor disposed of in other ways, but remain a long time unaltered at the point of inoculation and occasion smaller or larger abscesses.”

Koch proceeds to speak of the advantages of using an extract of the tubercle bacilli, the substance we now know as original tuberculin, which contains the curative substance, and from which the pus-producing substance is eliminated. He then goes on to give an explanation of the way in which tuberculin acts.

“Numerous hypotheses may be presented to explain the specific action of tuberculin upon tuberculous tissue. Without wishing to claim that my view is the best, I conceive the process to be as follows: Tubercle bacilli produce by their growth in living tissue, as well as upon artificial media, certain substances that act harmfully upon the neighboring cells. Among these there is one substance which in a given concentration kills living protoplasm and so alters it that it becomes transformed into the condition described by Weigert as coagulation necrosis. In this necrotic tissue the bacillus finds such unfavorable nourishment that it is unable to continue its growth and may finally die out. On this assumption I explain the fact that one finds numerous tubercle bacilli in freshly diseased organs, for example, in guinea pigs in the spleen or liver studded with gray tubercles, whereas they are scarce or absent in the hugely enlarged spleen which one frequently finds after the spontaneous death of tuberculous guinea pigs, and which con-

PRINCIPLES UNDERLYING USE OF TUBERCULIN

sists almost entirely of a whitish substance in the condition of coagulation necrosis. For the same reason, a small number of bacilli cannot produce extensive necrosis, for as soon as the necrosis has reached a certain point the growth of the bacilli is hindered and likewise the production of further necrosis. Thus a certain opposing compensation is established which occasions the restricted propagation of a small number of bacilli, as for instance in lupus, scrofulous glands, etc. In such cases the necrosis involves only a portion of the cell, which then by further growth takes on the peculiar form of giant cells. In this view I follow the explanation of the formation of giant cells first offered by Weigert.

“If we could artificially increase in the neighborhood of the bacilli the amount of necrosis-producing substance, the area of necrosis would be extended and thus the opportunity for the organisms to find nourishment rendered more difficult. This large area of necrotic tissue would then in part slough off, and if there be an outlet it and the inclosed bacilli would be ejected. The remaining organisms, living under unfavorable conditions, would be much more likely to die out than under normal conditions.

“It seems to me that the action of the remedy consists in the production of just such changes. It contains a certain amount of the necrotizing substance which in large enough doses damages tissue elements, probably the leukocytes or related cells, of even healthy individuals, thereby causing fever and the allied characteristic symptoms. In tuberculous individuals, however, even very small doses are sufficient to produce, with the accompanying results for the whole organism, more or less extensive cell necrosis in areas where living tubercle bacilli have already impregnated the surrounding tissues with the same necrotizing substance. In this way one can at least provisionally explain the specific action of the remedy in definite doses upon

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tuberculous tissues, the possibility of rapidly increasing these doses and the undeniable curative action of the remedy even under conditions that are only in a measure favorable.”

In his first communication following the announcement of the curative action of tuberculin Koch emphasizes these points:¹

“The substance is not active when taken into the stomach; to obtain reliable results it must be given subcutaneously. Man has a different relation to tuberculin from the guinea pig. While healthy guinea pigs may be given 2 c. c. and even more without showing any reaction, healthy men are profoundly affected by as little as 0.25 c. c.” Koch took this dose himself and thus describes his symptoms: “From three to four hours after the injection, pains in the limbs, depression, tendency to cough, dyspnea, the symptoms rapidly increasing in severity; after five hours an intense chill lasting almost an hour; at the same time nausea, vomiting, and rise of temperature to 39° C.; after about twelve hours the symptoms abated and the following day the temperature sank to normal; a feeling of weight in the limbs and depression persisted for several days and for the same length of time the point of injection remained red and painful.”

On the basis of numerous observations, he asserts that healthy individuals show a slight reaction to 0.01 c. c. Tuberculous individuals, however, have a violent general and focal reaction following such a dose, although not seriously affected by it, and after the reaction is over feel quite as well, indeed usually better, than before.

The focal reaction is best studied in lupus. A few hours after the injection the diseased skin becomes red and swollen. As the temperature rises, the swelling and

¹ Koch: Weitere Mittheilungen über ein Heilmittel gegen Tuberkulose. Deutsch. med. Wehnschr., 1890, xvi, 1029.

PRINCIPLES UNDERLYING USE OF TUBERCULIN

redness increase and may reach such a marked degree that the tissue becomes brownish red and necrotic. With the fall of temperature the swelling decreases and in a few days may completely disappear. The lupus areas are covered with crusts which dry and fall off, leaving, sometimes after a single injection, a smooth pink scar. It is remarkable how absolutely specific is the selection of tuberculin for tuberculous tissue, none of the surrounding skin or old scars showing the least evidence of reaction.

This same reaction no doubt occurs in the lungs, although it is difficult to get evidence of it. In tuberculous glands, bones and joints, increased swelling, pain, and often redness are apparent. Based on these observations, Koch lauds tuberculin as an important diagnostic agent and as a satisfactory means of deciding whether a previous lesion is completely healed or not. In speaking of tuberculin in treatment he further says: "The remedy kills the tuberculous tissue, not the tubercle bacilli. This limits accurately its action. It is capable of influencing only living tuberculous tissue; upon dead tissue, for instance cheesy masses, necrotic bone, etc., it has no action; likewise none upon the tissue killed by the substance itself. In such dead tissue masses of living tubercle bacilli may be contained which are thrown off with the necrotic tissue or under special conditions gain another foothold in the neighboring living tissue." In cases where surgical interference is possible it will assist the cure by getting rid of such necrotic masses.

Koch ascribes the ease with which patients are rapidly accustomed to increasing doses of tuberculin to this necrotizing action, which rapidly decreases the living tuberculous tissue upon which tuberculin can act.

For the treatment of pulmonary tuberculosis he recommends giving 0.001 c. c. as the initial dose and to rapidly raise the amount. He describes the results thus: "The

THE TUBERCULIN REACTION

action of the substance was in general manifested by an increase of cough and expectoration after the first few doses, followed by a steady decrease and, in favorable cases, complete disappearance. The sputum, too, lost its purulent character and became mucoid. The number of bacilli—and only those patients were chosen for treatment who had bacilli in the sputum—as a rule first began to decrease as the sputum became mucoid in appearance. They were then temporarily missed, but later were again found from time to time until the sputum completely disappeared. Coincidentally night sweats ceased, the general appearance improved and the patients increased in weight. All of the patients in the early stages of tuberculosis were free of symptoms after from four to six weeks so that they could be looked upon as cured. Patients with not too large cavities were likewise greatly improved and almost cured. Only in patients with many and large cavities in their lungs was no objective change noted, although even in these the symptoms decreased and the general condition improved.” Koch further strongly emphasizes that far advanced cases with complications are unsuitable for treatment and that general hygienic measures are a valuable aid in bringing about the cure. He reiterates that “the crux of the new method of cure lies in its earliest possible application,” and concludes: “Only then will the new method have become a genuine blessing for suffering mankind, when it will have come to pass that all cases of tuberculosis are taken early under treatment, and the occurrence prevented of advanced, neglected cases, which up to the present have formed the inexhaustible source of ever-recurring infection.”

Koch then in his original communication has given us a classical picture of the tuberculin reaction characterized, as are all his descriptions, by accurate observation and a simple, direct presentation. He failed to appreciate the true significance of the reaction at the site of injection, al-

PRINCIPLES UNDERLYING USE OF TUBERCULIN

though its occurrence is carefully noted. It is this local reaction which has come to assume such importance in recent tuberculin applications, both for diagnosis and treatment, and has played so prominent a part in the development of our ideas of immunity processes in tuberculous disease. For purposes of emphasis we recapitulate that a reaction to tuberculin is characterized by three essential features:

1. A constitutional reaction, consisting of temperature elevation and concomitant general symptoms varying in severity with the intensity of the reaction.

2. A local reaction, consisting of an inflammatory nodule at the site of injection. This varies in intensity from slight tenderness and redness to large masses of infiltration, often associated with swelling of the neighboring glands.

3. A focal reaction, consisting of an inflammatory reaction at the site of the lesion, so well described by Koch in lupus.¹

We will not stop to consider in detail the variations in these three factors. This will be done fully in the discussion of the application of the tuberculin reaction to diagnosis. It suffices to say that they by no means run parallel, there frequently being an intense local reaction with no or only slight constitutional symptoms and that in most instances, and particularly in slight pulmonary lesions, signs indicating a focal reaction are seldom conclusively appreciable. It is to be supposed that Koch's suggestions about the manner in which tuberculin acts have not held fast in the stream of fresh knowledge the past twenty years have

¹ The terms "local" and "focal" reaction are not always applied according to these definitions. In older contributions the term local reaction nearly always means the reaction at the site of the disease, and in the German literature local and focal are used interchangeably, the reaction at the site of injection being spoken of as the "stichreaktion." It is important to emphasize that we will adhere rigidly to the definition here given.

THE SPECIFICITY OF THE TUBERCULIN REACTION

poured out. As explanations, they no longer meet the demands of later experience. We shall try to outline briefly of what this experience consists and in how far it has changed or modified Koch's views.

As we have said, Koch assumed that tuberculin is a substance toxic for human beings, although its specific action in minute doses is manifested only when they harbor a tuberculous lesion. He notes in this respect a marked difference between the susceptibility of healthy human individuals and of healthy guinea pigs, the latter tolerating with impunity injections of two cubic centimeters and more, while even healthy men will show some reaction to as little as 0.01 c. c. Undoubtedly tuberculin is not an innocuous substance and Römer,¹ in a recent publication, agrees with Koch in so far as he insists that one must call the reacting power of an individual to tuberculin not sensitiveness but hypersensitiveness to tuberculin. When, however, Koch places the dividing line between sensitiveness and hypersensitiveness at ten milligrams, and makes human beings at least fifteen hundred times more sensitive than guinea pigs, we must part company with his views, and for the following well-established reasons:

THE SPECIFICITY OF THE TUBERCULIN REACTION

There is now little zest to a discussion of the specificity of the tuberculin reaction because the question has been settled to the satisfaction of nearly every one. Still, the question has played an important rôle in the history of the tuberculin reaction and it is of such fundamental importance to show just what a reaction, or the absence of reaction, to tuberculin indicates, that we cannot pass it by without notice. In the earliest era of tuberculin use it was ob-

¹ Römer and Joseph: Experimentelle Tuberkulose Studien. Beitr. z. Klin. d. Tuberk., 1910, xvii, 430.

served that not only the manifestly tuberculous, but many affected with other disease and indeed healthy individuals, gave a reaction to the injections. Köhler and Westphal¹ reported reactions to from 3 to 10 milligrams of tuberculin in four individuals with wounds and scars in whom there was no suspicion of tuberculous disease. The patients had marked constitutional symptoms but showed no reaction about the wounds or scars, and in the absence of a focal reaction Köhler and Westphal see the distinguishing feature from true tuberculous skin lesions. v. Leyden² notes that some healthy individuals react and some advanced tuberculous do not. Maydl reports³ that, of six healthy individuals, three reacted. Peiper⁴ is apparently the first to have made this particular question the specific object of an investigation. Of twenty-two patients with disease other than tuberculosis and in whom tuberculosis could clinically be excluded, eighteen reacted to subcutaneous injections of ten milligrams or less of tuberculin.

The multiplication of similar observations soon led to a distrust of the specific action of tuberculin. The explanation which we now know to be so simple was not thought of because the admirable anatomical studies upon which it is based are of more recent date. But before human pathology shed the necessary light upon this field of apparently inextricable contradiction, the question was being satisfactorily settled by veterinary practice. Tuberculin early became extensively used to determine the presence of tuberculosis in cattle and here were given ideal conditions for deciding its value; for the results of the test were immedi-

¹ Köhler and Westphal: Ueber die Versuche mit der von Herrn geheimrath Koch gegen Tuberculose empfohlenen mittel. Deutsch. med. Wehnschr., 1890, xvi, 1058.

² v. Leyden, cited by Peiper.

³ Maydl, cited by Peiper.

⁴ Peiper: Ueber die Wirkung des Koch'schen Mittels auf gesunde oder nichttuberculöse Individuen. Deutsch. med. Wehnschr., 1891, xvii, 160.

ately controlled by the autopsy findings. Fränkel¹ collected from the literature 8,000 carefully observed instances and found only from two to three per cent. difference between the results of the tuberculin test and of the autopsy. Voges² in 7,327 instances noted 2.7 per cent. of contradictions. Kühnau,³ Bang⁴ and v. Behring⁵ speak of their experience as equally convincing.

These investigations show that, apart from certain well-recognized sources of error, the tuberculin test in cattle gives results in absolute accord with autopsy findings. On account of their far-reaching importance and complete applicability to human pathology, we enumerate the sources of error:

1. Errors in interpretation of what constitutes a reaction to tuberculin. In cattle, temperature elevation has been made the decisive symptom, and when this is not high it may leave one in doubt. This is particularly true, if every source of mistake be not carefully guarded against. Römer⁶ has observed, for example, that cattle brought from the fields and confined in a stall for the purpose of tuberculin diagnosis often have fever for several days without apparent cause. Causes independent of tuberculin may concomitantly produce temperature elevation and so occasionally lead to a false interpretation. Cattle raisers have frequently, for purposes of deception, forced the tested stock to drink large quantities of cold water, or have

¹ Fränkel: Das Tuberculinum Kochii als Diagnosticum. Ztschr. f. Tuberk., 1900, i, 291.

² Voges, cit. Köhler: Tuberculin und Organismus. Jena, 1905, 77.

³ Kühnau: Berliner tierärztl. Wochenschr., 1899, cit. Köhler, 78.

⁴ Bang: Studies on tuberculosis in domestic animals, and what we may learn from them regarding human tuberculosis. Sixth International Congress on Tuberculosis. Special Volume, 1908, 211.

⁵ v. Behring: Beitrag zur Frage der Rindertuberculose Immunisirung. Beitr. z. exper. Therap., 1905, x, 1-21.

⁶ Römer: Tuberkulose und Tuberkulinreaktion. Beitr. z. Klin d. Tuberk., 1910, xvii, 427.

given cold water irrigations, immediately before the temperature is taken, thus preventing the registration of what fever may have been present.

2. Errors due to artificial immunization. It has long been known that previous tuberculin injections may so reduce an animal's hypersensitiveness that it will fail to react to the usual diagnostic dose. Gutman¹ has verified this experimentally and practically the method has been widely used in Denmark, France and elsewhere to render hypersensitive animals, destined for exportation into Germany, refractory to tuberculin. Germany has a law requiring that all cattle brought into the country must successfully pass the tuberculin test. In regions where many calves are immunized according to the method introduced by v. Behring and Koch, namely, by the injection of living human tubercle bacilli, misinterpretation must be guarded against, as such animals acquire tuberculin hypersensitiveness which persists for some time.

These two sources of error it is possible to guard against, and in the collected statistics they have played probably an insignificant rôle. The two following are the important factors in the disagreement:

3. A positive reaction with anatomically no tuberculous lesion. What is most striking in the results of the tuberculin test in cattle is (a) the great frequency of reaction in even apparently healthy animals and (b) the minute lesions that may be the cause of such hypersensitiveness. With this second point firmly fixed in our minds, we are prepared to grant that in certain instances it may be impossible to find a tuberculous focus, although it be present, and indeed we are surprised that they should be so consistently discovered. The lack of agreement between positive test and

¹ Gutman, cit. Römer: Das Tuberkulin in seiner diagnostischen Anwendung bei Tieren. Kraus and Levaditi: Handbuch der Technik und Methodik der Immunitätsforschung, 1908, i, 1080.

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autopsy is so infrequent, that it seems to us the only valid explanation of these exceptions is to refer them to the incompleteness of the autopsy. Indeed, we have come to rely so confidently upon the evidence of tuberculin in seeking a hidden tuberculous infection, that the autopsy must carry the burden of proof and blame.

4. A negative reaction when anatomically tuberculosis is present. This is a far more frequent and important source of error. The conditions under which it may occur are:

a. When the disease is far advanced. If the animals are carefully examined and clinically observed, the importance of this factor is greatly diminished, indeed practically obliterated.

b. When tuberculous lesions have become completely healed. One cannot, however, tell anatomically in a given instance whether hypersensitiveness was present or absent.

Before the tuberculin era, it was well understood that tuberculosis in cattle was far more common than clinical study of herds would indicate. At the Copenhagen abattoir 16 per cent. to 18 per cent. of slaughtered animals showed foci of disease; at Leipzig over 20 per cent. Neither cattle raisers nor veterinarians were, however, prepared for the astonishing revelations of the tuberculin test. "When the tuberculin tests in 1891 and 1892 showed that, in herds in which for years cases of the disease had been found, a majority of the cases (often 80 to 100 per cent.) reacted, it was not clearly understood that these great numbers meant simply that the majority of the cases were infected, but by no means signified that the reacting cases were sentenced to death, and after a longer or shorter period would succumb to tuberculosis. This great number of reacting cases made the farmer despair. He had perhaps, in the course of many years, raised a fine and productive herd, and now everything seemed lost. The cows would perish, and how

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could he maintain the stock when he was afraid to raise calves from tuberculous animals? He often regarded himself as ruined. It soon appeared that the majority of reacting animals suffered only from a very limited, often quite insignificant, form of tuberculosis, and by observing the fate of such animals (as I had an opportunity of doing with a large herd in which the reacting animals were allowed to live and I examined them all when they were eventually slaughtered) it was seen that in many of them the disease did not develop further, but, on the contrary, tended to decrease."¹

The crucial point of the results, a point we shall not tire of repeating, is that tuberculin indicates infection and not disease in a clinical sense. Note that many, indeed most, of the reacting cattle were apparently quite healthy, and, if allowed to live, they remained healthy and did not develop symptoms of tuberculous disease, at autopsy showing inactive or regressing lesions.

It is remarkable that these results so early and definitely established for cattle should not have been applied to man. Parallel conditions existed. It was noted that the definitely tuberculous reacted, although many advanced cases did not. The latter fact was explained upon the theory of Koch and Ehrlich that the tissues had become too saturated with the tuberculin produced at the infected area to respond to further artificial additions. But the contradictory evidence obtained among healthy individuals, and those suffering from disease other than tuberculosis, led only to confusion. Many failed entirely to react; others reacted to small doses; others again reacted to ten milligrams and still others only to fifty, a hundred or two hundred milligrams. Numerous explanations were offered to

¹ Bang: Studies on tuberculosis in animals and what we may learn from them regarding human tuberculosis. Sixth International Congress on Tuberculosis. Special Volume, 1908, 211.

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account for these divergent facts. Rosenbach¹ suggested that the reaction depended on the instability of the heat-regulating mechanism of tuberculous patients, and could be produced as well by numerous other bacterial products. Likewise that tuberculin is not specific, for it will cause fever in convalescents and patients in a weakened condition, as readily as in the tuberculous. The frequency with which patients suffering from disease other than tuberculosis reacted led to grouping certain diseases as producing the conditions necessary for response. Chief among these was syphilis. In leprosy the conditions require special consideration. The bacillus of leprosy is closely related to the tubercle bacillus and reactions in leprosy may be the expression of a group reaction, just as are the reactions of the tuberculous to the products of hay and other acid-fast bacilli. To our knowledge, no direct proof of this assumption has been advanced but we must admit its possibility. Similar views were held in reference to actinomycosis, but Friedrich² has reported an instance of extensive actinomycosis of the liver with positive tuberculin reaction, where autopsy revealed a tuberculous pulmonary lesion that had escaped clinical detection. He feels that there is not sufficient evidence upon which to conclude that actinomycosis alone ever produces tuberculin hypersensitiveness. This has gradually come to be the attitude toward all the diseases formerly supposed to engender it. Two special lines of research have occasioned the change. First, more carefully collected anatomical statistics upon the frequency of tuberculosis in man; and, second, statistical studies of the tuberculin test administered to a large number of individ-

¹ Rosenbach: Einige Gesichtspunkte zur Beurtheilung des Koch'schen Verfahrens nebst Bemerkungen über Einfluss antipyretischer Maassnahmen auf der Reactionsfieber. Deutsch. med. Wehnschr., 1891, xvii, 309.

² Friedrich: Tuberkulin und Aktinomykose. Centralbl. f. Chir., 1896, xxiii, 1096.

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uals, healthy, tuberculous, and suffering from other diseases.

As in animal pathology, so in human, it had been frequently noted and commented upon that the occurrence of tuberculosis anatomically far exceeded in extent its recognition clinically. Lebert¹ emphasized this and Baumgarten¹ estimated that one in every third corpse showed a latent or healed tuberculous focus. Bollinger,¹ too, has commented that about one-fourth of all adult bodies show suspicious or evident tuberculous processes of the pulmonary apices. However, no real notion of its extent existed before the remarkable statistics published in the past twelve years. Schlenker² in 1893 made a careful gross examination of 100 bodies and discovered tuberculosis in 66. In 35 instances, 53 per cent., tuberculosis was the cause of death; in 4 instances, 6 per cent., the tuberculosis was extensive, but not the cause of death; in 27, 41 per cent., he found inactive or latent tuberculosis. Schlenker himself suggested that higher percentages would be found upon more exact investigation as he only occasionally had recourse to microscopical examination. This prediction was verified when Nägeli's studies appeared in 1900.³ In 508 instances, all carefully observed, 406 gave evidence of tuberculous infection. In 88 sections upon children up to 18 years of age 15, 18 per cent., were tuberculous, and in 10 of the 15, 66 2-3 per cent., tuberculosis was the cause of death; of 420 adults 391, 93 per cent., showed evidence of tuberculosis and in 110, 28 per cent., tuberculosis was the cause

¹Lebert, Baumgarten, Bollinger, cited Cornet: *Die Tuberkulose*. Wien, 1907, i, 370.

²Schlenker: *Ueber die Häufigkeit tuberculöser Veränderungen in menschlichen Leichen*. Virchows Arch. f. path. Anat., 1893, cxxxiv, 145.

³Nägeli: *Ueber Häufigkeit, Localisation und Ausheilung der Tuberkulose nach 500 Sektionen des Züricher Pathologischen Institut*. Virchows Arch. f. path. Anat., 1900, clx, 426.

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of death. Burkhardt's figures,¹ presented at Dresden in April, 1903, and published in full in 1906, corroborated Nägeli's results and are more important because they embrace a larger number of autopsies, namely, 1,452. The



FIG. I.—COMPOSITE CHART OF BURKHARDT'S ANALYSIS OF 1,452 AUTOPSIES.

----- Latent inactive tuberculosis
 o o o o o Latent active tuberculosis
 - - - - - Fatal tuberculosis.
 - o - o - o Total amount of tuberculosis.

composite chart shows graphically the most important of Burkhardt's results. The points are notably:

1. The increased frequency of tuberculous infection with advancing years, reaching over 90 per cent. past the 18th year.

2. The great fatality of tuberculosis during the first few years of life and its extreme death rate in early adult life.

3. The steady and rapid rise with years in the fre-

¹ Burkhardt: Häufigkeit und Ursache menschlicher Tuberkulose auf Grund von ca. 1400 Sektionen. Ztschr. f. Hyg. u. Infektionskrankh., 1906, liii, 139.

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quency of latent active and particularly latent inactive tuberculosis.

It is scarcely necessary to refer to Cornet's¹ inconsequent criticism of Burkhardt's and Nägeli's figures, for the recent results with tuberculin tests have fully corroborated their statistics.

Hamburger² published the following results of an analysis of 848 autopsies on children:

| | | | | |
|-------------|--------|---------------|-----------------|------------|
| 0 to 3 mon. | of age | 105 sections: | Tuberculosis in | 4= 4% |
| 4 " 6 " | " " | 73 " | " " | " 13=18 " |
| 7 " 12 " | " " | 140 " | " " | " 32=23 " |
| 1 " 2 yrs. | " " | 179 " | " " | " 74=40 " |
| 3 " 4 " | " " | 175 " | " " | " 102=60 " |
| 5 " 6 " | " " | 67 " | " " | " 38=56 " |
| 7 " 10 " | " " | 65 " | " " | " 41=63 " |
| 11 " 14 " | " " | 44 " | " " | " 31=70 " |
| <hr/> | | | | <hr/> |
| | | 848 " | " " | " 335=40% |

In 617 cases tuberculosis was not the cause of death but was found incidentally at autopsy as follows:

| | | | | |
|-------------|--------|---------------|----------------------------|-----------|
| 0 to 3 mon. | of age | 102 sections: | Incidental Tuberculosis in | 0= 0% |
| 4 " 6 " | " " | 60 " | " " | " 0= 0 " |
| 7 " 12 " | " " | 114 " | " " | " 5=4.5 " |
| 1 " 2 yrs. | " " | 126 " | " " | " 22=17 " |
| 3 " 4 " | " " | 106 " | " " | " 33=30 " |
| 5 " 6 " | " " | 44 " | " " | " 15=34 " |
| 7 " 10 " | " " | 37 " | " " | " 13=35 " |
| 11 " 14 " | " " | 28 " | " " | " 15=33 " |
| <hr/> | | | | <hr/> |
| | | 617 " | " " | " 103=17% |

Of tuberculin test statistics we call particular attention to those of Fraenkel, Franz and Beck. We shall have occa-

¹ Cornet: Die Tuberkulose. Vienna, 1907, i, 371.

² Hamburger: Zur Kenntnis der Tuberkuloseinfektion im Kindesalter. Wien. klin. Wchnschr., 1907, xx, 1070.

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sion to refer to them in another connection¹ of greater practical importance and state them here briefly. Fraenkel reports 200 observations; of 56 tuberculous cases all reacted; of 76 suspected cases 70 reacted; of 68 unsuspected patients 37, or 56 per cent., reacted. Franz injected 400 recruits of the Bohemian Army, healthy young men who had passed their entrance examination, and found that 61 per cent. reacted. Beck reports observations on 2,508 patients, and of these, 1,525, or 60.8 per cent., reacted; 371 were definitely tuberculous and all reacted; 423 were suspected of having tuberculosis and of these 364, or 86 per cent., reacted; 1,714 were convalescent, or patients ill with other disease, and of these 790, or 46.1 per cent., reacted. There is a remarkable correspondence between the results of Beck and the figures obtained anatomically by Burkhardt.

With these results prominently before them, clinicians still failed to consequentially apply the information to their practical work. The original ideas of Koch clung too fast to be easily discarded and as late as 1904 Goetsch, Bandelier and others seriously discuss the dose at which healthy individuals will react, and Löwenstein and Rappoport write: "In the literature there is an absolute accord upon the fact that healthy individuals react to tuberculin."² Bandelier³ found that, of twelve cases negative to 10 mg., four reacted to 20 and six to 50 mg. From this evidence he concludes that even healthy individuals will react to 20 mg. of tuberculin, although why he should not agree with Goetsch⁴ in selecting 50 mg. as the dividing line is difficult

¹ See p. 102.

² Löwenstein and Rappoport: Über den Mechanismus der Tuberkulinimmunität. Ztschr. f. Tuberk., 1904, v, 486.

³ Bandelier: Die Tuberkulindiagnostik in den Lungenheilstätten. Beitr. z. Klin. d. Tuberk., 1904, ii, 285.

⁴ Goetsch, cit. Bandelier, *ibid.*

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to see. It would have been instructive had he proceeded with the remaining two cases and determined at what dose they would react. The only proof that these twelve cases were healthy is that they failed to react to ten milligrams of tuberculin, for clinically they were equally as suspected of having tuberculosis as were many hundred other cases that did react. The argument is, to say the most of it, naïve. It remained for the investigations of Hamburger to bring the final and convincing proof.

The use of tuberculin immediately after its introduction at once led to the observation that children, and particularly infants, are remarkably refractory to its influence. While adults almost regularly reacted to 10 mg., infants failed to react to such doses and indeed often showed no reaction to large amounts. Thus, Epstein¹ regularly obtained negative results to 1 and 2 mg. and Schreiber, whose observations were made upon forty new-born infants, never produced a reaction even with 50 mg. On account of the great interest of the question and his very clear results, we quote as follows: "I have demonstrated that one may in new-born infants rapidly raise the dose to 15 mg. without obtaining the slightest suggestion of a reaction. Healthy adults will almost without exception give a severe reaction to such a dose. Later, I raised the dose by 10 to 20 mg. so that on the third or fourth injection I have given 50 mg. Following even such large doses, there has been no trace of reaction. In new-born infants I have never seen a skin infiltration develop (local reaction), indeed nothing that could be interpreted as a change in their general condition. How to explain this is an open question, but I surmise that the cause of the very remarkable relation is to be sought in the active metabolism of the infant. For to-day suffice the presentation of this very interesting

¹ Epstein, cit. Hamburger, loc. cit., p. 17.

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fact.”¹ Similar results are reported by Berend² in 1900, although he does not go beyond 10 mg.

This, as Schreiber speaks of it, very remarkable condition became a matter of general observation and some unknown difference between the constitution of the child and the adult was conjured up to explain it. In what the difference consists, however, is clearly shown by Hamburger. Hamburger³ presents observations upon forty-three children between 0 and 14 years of age. After determining that they fail to react to the cutaneous test and give no local reaction after injections he, in rapidly succeeding doses, administers up to 500 mg. of tuberculin without producing the slightest reaction. It is futile to object that the children acquire tolerance from the foregoing injections. The intervals are too short and the jumps too large to permit such an interpretation.

We see now very clearly the source of the conflicting and bewildering results. Healthy adults do react to tuberculin, but they react because they have a tuberculous lesion. Among those who react there is, as the earliest experience demonstrated, the greatest variation in sensitiveness, some reacting to 10 mg., some to 20, some to 50, and others to no less than 100 or 200 mg.

Convinced from the work of Hamburger that tuberculin has no appreciable effect upon uninfected individuals, we would be obliged, in order to establish the absence of such infection, to give a gram to infants and, estimating relatively by weight, ten to twenty grams to adults. Such a procedure has very manifest disadvantages, for those unfortunate enough to be unsuspectedly hypersensitive would

¹Schreiber: Koch's Heilmittel gegen die Tuberculose. Berlin, 1891, ii, 20.

²Berend, cit. Hamburger, loc. cit., p. 17.

³Hamburger: Ueber die Wirkung des Alttuberkulins auf den tuberkulosefreien Menschen. München. med. Wehnschr., 1908, lv., 1220.

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suffer at least inconvenient results, and practically all adults are more or less hypersensitive. However, any discussion about doses which separate the healthy from the tuberculous is entirely done away with. In this connection we use the term healthy in quite a different sense from the one in which it was formerly employed. An individual may be healthy, indeed in excellent health, and still harbor a tuberculous lesion, and display a marked grade of hypersensitiveness to tuberculin. We do not speak of him as tuberculous until there are tangible symptoms referable to its existence, and thus draw a sharp distinction between infection and clinical manifestation which constitutes disease. In this sense, tuberculin is an index of tuberculous infection, not of tuberculous disease, and what this fundamental distinction implies for practice we shall later refer to in detail.

It has no doubt attracted comment that we have so far treated tuberculin hypersensitiveness very narrowly in considering only the constitutional symptoms as an index of its manifestation. We had previously spoken of three characteristics of a tuberculin reaction and then proceeded to disregard two. This has been occasioned by former attitudes toward tuberculin hypersensitiveness and the spirit in which the reports were made. We promptly offer amends by now stating that both the focal and the local reaction are of more importance than the constitutional reaction, and that the local reaction is less often misleading. There are certain possible sources of error in the interpretation of temperature elevation which have no counterpart in the determination of the local reaction. The reaction at the site of injection, first called attention to by Epstein, has since become generally known as the "Stichreaktion." In the early tuberculin era, regarded as an incidental accompaniment of the injection, it is only in the past few years that its absolute specificity and remarkable sensitiveness

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have been realized. Upon this local hypersensitiveness to tuberculin depend the cutaneous, conjunctival and other recent methods of application—methods that rely only upon the local reaction as a guide to susceptibility. Finally, the focal reaction is clinically the most decisive of all, for when ascertainable it stamps a lesion as definitely tuberculous and tells something of its extent and importance. Unfortunately, as we shall later have occasion enough to deplore, it is but seldom manifested in instances where its presence is most eagerly sought.

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We have quoted sufficiently from Koch to have made clear his views upon the mechanism of the tuberculin reaction. It is scarcely desirable to give in detail the numerous explanations that have been presented, but on account of their interest some of the most important will be briefly referred to. Having shown upon what secure evidence the specificity of the tuberculin reaction rests, we may merely mention that to many, following Rosenbach's lead, the reaction was merely an expression of thermal instability. The lively discussion concerning the employment of salt solution in place of tuberculin precipitated by Hutinel in 1895,¹ and waged with vigor until arrested by the conclusive results of Combemale and Mouton² in 1899, is only of historical interest. The first important attempt at an explanation upon a basis quite different from Koch's was by Matthes.³ Following up the observations of v. Jaksch and Rabitschek, who found albumoses in the urine of

¹ Hutinel: *Les effets des injections sous-cutanées chez les enfants tuberculeux*. *Semaine méd.*, 1895, xv, 117.

² Combemale et Mouton. *Cong. de Méd. Interne*. Lille, 1899.

³ Matthes: *Ueber die Wirkung einiger subcutan einverleibter Albumosen auf den thierischen, insonderheit auf den tuberculöse inficirten Organismus*. *Deutsch. Arch. f. klin. Med.*, 1894, liv, 39.

patients suffering from diseases accompanied by tissue destruction and notably in pulmonary tuberculosis, Matthes showed that, while healthy animals are unaffected by injections of small doses of deuterioalbumose, tuberculous animals react with high temperature elevation. Tuberculous animals react to 10 or 20 milligrams; healthy animals often tolerate a ten to fifty times larger dose. In man, twenty milligrams is always followed by temperature elevation. So clearly do the symptoms resemble those of a tuberculin reaction, that Matthes concludes the latter is principally an albumose intoxication. That tuberculin liberates symptoms in much smaller doses than albumose does, he ascribes to the peptone which is always present in it. He further notes that albumoses call forth local reactions where albumoses are already present. For instance, healthy animals invariably show hyperemia of the digestive tract while starving animals do not. As albumoses are regularly found in tuberculous foci, Matthes sees in their presence the explanation of the focal reaction. The constitutional and febrile reaction he thought to be due to a discharge of albumoses into the circulation consequent upon this reaction at the site of the disease.¹

Ehrlich² pictures the tuberculous focus as consisting of a central mass of bacilli secreting tuberculin. The tuberculin saturates the cells immediately about the bacilli, less reaching more distant cells. There are therefore consecutive layers of cells varying in tuberculin content from saturation to very small amounts. The surrounding healthy tissue and the saturated cells are insensitive to tuberculin, the reaction occurring in the cells whose resistance has been lowered by tuberculin, but not completely overcome. The

¹ Matthes: Ueber das Zustandekommen der fieberhafter Allgemeinreaktion nach Injektionen beim tuberkulösen Organismus. *Zentralbl. f. inn. Med.*, 1895, xvi, 385.

² Ehrlich: *Inter. Kongress f. Hygiene*, 1900, cited Köhler.

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focal inflammatory reaction he looks upon as the cause of the constitutional symptoms.

This view of Ehrlich's has been modified and put upon an attractive experimental basis by Wassermann and Bruck.¹ These investigators, using the method of complement fixation² that had previously given such brilliant results in the diagnosis of syphilis, were able to demonstrate in extracts of tuberculous foci the presence of a substance capable of uniting with such tuberculin. To this substance they gave the name antituberculin, but commit themselves to no definite view upon its nature other than to regard it as a specific reaction product of tuberculin stimulation. They likewise found that, while antituberculin is not present in the serum of healthy or tuberculous individuals, it may be demonstrated successfully in the serum of the tuber-

¹ Wassermann and Bruck: Experimentelle Studien über die Wirkung von Tuberkelbacillen—Präparaten auf den Tuberculöserkrankten Organismus. Deutsch med. Wehnschr., 1906, xxxii, 449.

² The method depends upon the following biological principles. The serum, for example of the rabbit, acquires the property of dissolving the red blood corpuscles of the sheep following several injections of sheep's corpuscles. If the serum of such an immunized rabbit be heated to 50° (inactivated) the lytic power is lost, but is immediately restored upon the addition of a small amount of normal rabbit serum. Thus three bodies play a part in the reaction. The sheep's corpuscles (antigen) injected into the rabbit stimulate the production of a specific antibody (substance sensibilitrice or amboceptor), which becomes active only in the presence of a substance normally found in the fresh unheated serum (alexin, complement). The virus of certain diseases (antigen) produces in the animal body a specific reaction body (amboceptor), which likewise, in the presence of the antigen, absorbs complement. If the disease antigen, in this instance supposedly tuberculin, be mixed with serum containing complement and with the heated serum of a patient presumed to have tuberculosis, and therefore possible reacting bodies, amboceptor, to tuberculin, the three unite and the complement is absorbed. If the patient's serum does not contain such specific amboceptors the complement is not bound and remains free in the mixture. To test the presence or absence of free complement a small amount of this mixture is added to a mixture of sheep corpuscles plus the inactivated (heated) serum of a rabbit immunized to sheep corpuscles. If the complement has been absorbed no hemolysis will occur; if still free the red blood corpuscles will rapidly be dissolved.

culous previously treated with tuberculin. On the basis of these observations, they look upon the reaction to tuberculin as depending upon a union of the injected tuberculin with the antituberculin at the site of the lesion. This combination anchors large quantities of complement which acts as a ferment upon the surrounding tissue, causing the inflammatory changes characteristic of the focal reaction, and these in turn determining the fever and other constitutional symptoms. When, following tuberculin injections, tolerance to large doses has been established, it is presumed that sufficient antituberculin is present in the serum to immediately unite with the tuberculin injected and thus prevent it from reaching the tuberculous focus. The reaction is frequently absent in cases of advanced tuberculosis because the cells, depleted by prolonged stimulation, are no longer able to respond with the production of sufficient antibodies.

The view of Wassermann and Bruck deserves and shall receive more extended notice, but we may begin by pointing out that all of these, and many other explanations that see the essential feature of the tuberculin reaction in the changes that occur about the area of disease, do not satisfy our present knowledge of tuberculin hypersensitiveness. For the presence of a tuberculous focus produces a profound change in all of the cells of the body. Not only does tuberculin then cause an inflammatory reaction about the lesion, but, applied to any of the tissues, similar local changes occur. Rubbed into the skin, injected into the subcutaneous tissue, or applied to the mucous membranes, pronounced and often violent reactions result. If we attempt to explain these local reactions as an evidence of the union of tuberculin and antituberculin, we should look for their occurrence when the tuberculin is blocked off from the site of disease and the general and focal reaction thus prevented. In artificially produced tuberculin immunity, how-

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ever, local reactions never appear and, furthermore, in those tuberculous cases in which Wassermann and Bruck find no antituberculin in the serum they are particularly well marked. As we shall later point out, the local reactions roughly run parallel to the general tuberculin hypersensitiveness, which coincidence it is difficult to explain upon their hypothesis.

As the reaction at the seat of the lesion plays an essential rôle in the Wassermann-Bruck conception, it may be advisable to point to what evidence we have bearing upon the relation of the focal changes to the general symptoms. That there is some relation between the two cannot be doubted and still there is evidence indicating that the general reaction is not entirely dependent upon the focal. Baldwin was able to show in one rabbit that extirpation of the tuberculous focus was followed by a rapid loss of tuberculin hypersensitiveness.¹ Bahrddt² found that excision of a portion of the tuberculous area in guinea pigs causes a decrease in tuberculin sensitiveness. Preisich and Heim³ introduced colloidin sacs containing tubercle bacilli into the peritoneal cavity of guinea pigs and in from twelve to sixteen days obtained a definite reaction to tuberculin. At autopsy the sacs were found firmly closed and no infection of the animals had occurred. They further found that by injecting tuberculous material and tuberculin simultaneously no reaction developed. Baldwin conducted similar experiments, inclosing bacilli in Berkefeld filters, and does not regard the evidence of tuberculin hypersensitiveness that he obtained as conclusive. However, that hypersensitiveness does occur under such conditions seems to be sat-

¹ Baldwin: Studies on the tuberculin reaction. Studies from the Saranac Laboratory, 1900 to 1904.

² Bahrddt: Experimentelle Untersuchungen über die Tuberkulinreaktion. Deutsch. Arch. f. klin. Med., 1908, lxciii, 232.

³ Preisich and Heim: Ueber das Wesen der Tuberkulinreaktion. Centralbl. f. Bakteriologie, 1902, xxxi, 712.

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isfactorily determined by the extensive observations of Heymans.¹ This investigator has sought to produce immunity to tuberculosis in cattle by introducing, beneath the skin, diffusible sacs containing tubercle bacilli. Animals inoculated with such sacs show characteristic tuberculin hypersensitiveness after from three to six weeks, which is again lost in from six to eight months. While so much must be granted, this fact does not establish the independence of the tuberculin reaction from the changes in the focus of disease, for Heymans has shown that about these sacs typical tuberculous infiltration is formed. Lastly we note that cattle immunized with living human tubercle bacilli, after the method of v. Behring and Koch, acquire a high grade of tuberculin hypersensitiveness, although no gross tuberculous foci develop. Here again probably small tubercles are formed. What we may conclude from these experiments and from clinical observation is that sensitiveness does not run parallel with the extent of the lesion and that caseation is not necessary for its development.

We cannot doubt that, under certain conditions, substances appear in the blood of tuberculous patients which unite with tuberculin and anchor complement. There is, however, divided opinion about the constancy with which they appear under given conditions and their specific character. Weil and Nakajama,² shortly following Wassermann and Bruck's publication, point out that it is difficult to understand how tuberculin and antituberculin can exist together in a tuberculous focus without neutralizing one another. They show that tuberculin and tubercle bacilli extracts alone absorb complement and believe that in the Wassermann-Bruck procedures tuberculin and tissue ex-

¹ Heymans: Vaccination gegen Tuberkulose beim Rinde. Sixth International Congress on Tuberculosis, 1908, iv, pt. 2, 997.

² Weil and Nakajama: Ueber den Nachweis von Antituberkulin im tuberkulösen Gewebe. München. med. Wehnsehr., 1906, liii, 1001.

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tracts are present in large enough amounts to prevent hemolysis without compelling the assumption of the presence of specific tuberculin antibodies. Wassermann and Bruck¹ reply by admitting that tuberculin in large quantities does of itself absorb complement, but add further instances in which such small amounts are used that the resulting inhibition of hemolysis, they believe, demonstrates conclusively the presence of antituberculin. Lüdke² finds antituberculin in tuberculous tissues and in the blood of patients treated with tuberculin. He further finds that albumoses will replace tuberculin as antigen and the serum of animals treated with albumoses possesses amboceptor which unites with tuberculin and fixes complement. He sees in this a valuable confirmation of the view that the albumose content of tuberculin is the active portion. Cohn³ points out that antituberculin occurs frequently in the blood of patients not treated with tuberculin, although he has never observed the reaction in tuberculosis-free individuals. He was unable to find any relation between the presence of antituberculin in the serum and the degree of tuberculin hypersensitiveness of the individual.

Morgenroth and Rabinowitch,⁴ although fully confirming Wassermann's work in syphilis, contend that the method applied to tuberculosis is too coarse and open to too many sources of error to be reliable. Following the specific directions of Wassermann and Bruck, they obtain only negative results. They point out that complement

¹ Wassermann and Bruck: Ueber das Vorhandensein von Antituberkulin im tuberkulösen Gewebe. München. med. Wehnschr., 1906, liii, 2396.

² Lüdke: Über den Nachweis von Antituberkulin. Beitr. z. Klin. d. Tuberk., 1907, vii, 47.

³ Cohn: Über die durch Komplementbindungsnachweisbaren Tuberkulose-Antikörper im Blute von Phthisikern. Beitr. z. Klin. d. Tuberk., 1908, xi, 143.

⁴ Morgenroth and Rabinowitch: Die Immunitätsreaktion tuberculösen Gewebes und deren Zusammenhang mit der Therapie der Tuberkulinwirkung. Deutsch. med. Wehnschr., 1907, xxxiii, 705.

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acts lytically only upon the substance to which it is bound and therefore could not be assumed to produce a focal reaction. To Lüdke's results with albumoses they object that the albumose in the culture media may be the reacting body.

Citron¹ finds that antituberculin occurs, but not regularly, in the tuberculous. Patients treated with tuberculin who tolerate large doses and lose their hypersensitiveness almost regularly show antituberculin in the serum, while those in whom hypersensitiveness persists seldom have it.

Weil and Straus² could demonstrate antituberculin in many tuberculin-treated and some untreated tuberculous cases. Contrary to Citron they find antituberculin in the serum even when a high grade of hypersensitiveness is present.

Cohn³ examined 77 patients. In 10 clinically not tuberculous he found no antibodies. In 14 cases classed as of the first stage, likewise none. In 53 cases of open tuberculosis in the second and third stage, 15 had antituberculin in the serum without previous tuberculin treatment. Even large quantities of antituberculin in the serum do not inhibit a tuberculin reaction. He finds no relation between antituberculin in the serum and hypersensitiveness to tuberculin.

Christian and Rosenblat⁴ found in the serum of healthy and tuberculous guinea pigs and rabbits no antituberculin. Healthy animals treated with bacillen emulsion likewise show none, while tuberculous animals treated with bacillen

¹ Citron: Ueber Tuberculoseantikörper und das Wesen der Tuberkulinreaktion. Berl. klin. Wehnschr., 1907, xlv, 1135.

² Weil and Straus: Ueber die Rolle der Antikörper bei der Tuberkulinreaktion. Wien. klin. Wehnschr., 1908, xxi, 1058.

³ Cohn: Ueber komplementbindende Tuberkulose-Antikörper und ihre Beziehungen zur Tuberkulinreaktion. Berl. klin. Wehnschr., 1908, xlv, 1309.

⁴ Christian and Rosenblat: Untersuchungen über Tuberkulose-Antikörper und Immunität. München. med. Wehnschr., 1908, lv, 2032.

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emulsion do. The authors do not consider the antibodies the factors in immunity, but merely its indication. They think the antibodies arise in the lymph glands, because the reaction ceases when the glands are removed.

Engel and Bauer¹ fail to find antituberculin in healthy and tuberculous infants. It is present only in those treated with large doses of tuberculin. Those patients who produce a large quantity of antituberculin recover.

Wolff and Mühsam² examined the serum of 109 tuberculous patients by the complement fixation method. 54 of the cases were advanced and 55 earlier cases. They could find no relation between the content of antituberculin in the blood and the gravity of the disease. A serum may be rich in antituberculin without the skin reaction being necessarily positive. They could find no constant relation between the amount of antituberculin and tuberculin treatment. They doubt the specificity of the reaction.

Noguchi³ found an almost constant complement fixation with the serum of tuberculous as well as non-tuberculous individuals. He further found by using peptone, albumose, glycogen and the extracts of numerous bacteria, tissues and organs, as well as numerous products of protein, that all of these substances fix complement. He thinks, then, that complement absorption is a property of all protein material and, in order that the reaction be specific, antigen should be used, from which the proteid substance is excluded. This is obtained in lues, for instance, by extracting the liver with acetone. He considers the reaction not specific.

¹ Engel and Bauer: Ueber die Bedeutung und die Spezifität der komplementbindenden Antikörper bei Tuberkulose und deren Beziehungen zu Heilungsvorgängen, 1908, lv, 2273.

² Wolff and Mühsam: Mit Tuberkulin komplementbindende Antistoffe im Serum Tuberkulöser. Deutsch. med. Wchnschr., 1908, xxxiv, 1504.

³ Noguchi: On non-specific complement-fixation. Proc. Soc. Exper. Biol. and Med., 1909, vii, 55.

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Rolly,¹ from observations made upon the serum of patients in all stages of pulmonary tuberculosis, is inclined to question the specificity of the reaction.

Fua and Koch² found no antituberculin in the serum and cerebrospinal fluid of untreated cases, while they could demonstrate its presence in one-third of the tuberculin-treated children.

Simon and Hanns³ found absence of hemolysis in tests made with the serum of 124 cases of pulmonary tuberculosis 18 times and found no complement fixation in the serum of normal individuals.

Slatinéanu and Danielopolu⁴ find fixation much more commonly in the pleural and peritoneal exudate of the tuberculous than in the blood serum.

Armand-Delille⁵ finds, in contradistinction to other investigators, an absolute accord between the complement fixation power of the serum and the tuberculin hypersensitiveness as measured by the cutaneous test.

Bach⁶ shows that the serum of tuberculous and non-tuberculous cattle gives the complement fixation test in about the same number of cases. He thinks it has absolutely no value in diagnosis. One cannot even find greater quantities of antituberculin in the tuberculous than in the non-tuberculous cattle.

¹ Rolly: Die Wassermannsche Seroreaktion bei Lues und anderen Infektionskrankheiten. München. med. Wehnschr., 1909, lvi, 62.

² Fua and Koch: Zur Kenntnis der mit Tuberkulin komplementbindenden Stoffe im Serum tuberkulöser Kinder. Beitr. z. Klin. d. Tuberk., 1909, xiv, 79.

³ Simon and Hanns: Recherche des anticorps tuberculeux dans le sérum humain par la méthode de la déviation du complément. Internat. Centralbl. f. d. ges. Tuberk.-Forsch., 1909, iii, 484.

⁴ Slatinéanu and Danielopolu: Présence du fixateur dans les exsudats pleuraux et péritonéaux d'origine tuberculeuse. Ibid., 485.

⁵ Armand-Delille: Déviation du complément à la tuberculine et cutiréaction. Ibid., 706.

⁶ Bach: Systematische Untersuchungen über die Brauchbarkeit der Komplementbindungsmethode für die Serumdiagnose der Tuberculose des Rindes. Thèse inaug. École vétérinaire, Dresden, 1909.

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Laub and Novotny¹ examined 134 specimens of serum, 104 from the cadaver, 30 from tuberculous patients. Only 4 of these 30 gave a definite reaction. Of 20 specimens, taken after the death of tuberculous patients, only one gave a definite reaction. Of 70 specimens coming from cadavers showing absolutely no tuberculous lesion, 11 gave the reaction. They conclude, therefore, that the reaction is not at all specific.

Bezançon and Sorbonnes² emphasize the inconstancy of the reaction in the tuberculous. It often runs irregularly in the same individual, its loss often coinciding with an aggravation of the symptoms. The reaction does not run parallel with the agglutinating and precipitating power.

About the nature of antituberculin we can say that it is not an antibody in the sense of being an antitoxin. Single or repeated injections of large or small amounts of tuberculin in healthy animals never occasion tuberculin hypersensitiveness, nor do they cause antituberculin to appear in the serum. Whether mixed with tuberculin they inhibit its activity is as yet unsettled. Pickert and Löwenstein³ found that the serum of tuberculous patients who under treatment had developed marked tolerance for large doses of tuberculin inhibits the production of the cutaneous reaction when mixed with tuberculin in the proportion of nineteen to one. Serum from normal individuals does not possess this power. They found, however, that in a small number of cases the reaction remained uninfluenced. White

¹ Laub and Novotny: Ueber komplementbindende Substanzen bei Tuberkulose. Wien. klin. Wchnschr., 1909, xxii, 1104.

² Bezançon and Sorbonnes. Remarques sur le pouvoir antagoniste du sérum normal et de divers substances qui entrent en jeu au cours de la réaction de fixation. Internat. Centralbl. f. d. ges. Tuberk.-Forsch., 1910, iv, 183.

³ Pickert and Löwenstein. Eine neue Methode zur Prüfung der Tuberkulinimmunität. Deutsch. med. Wchnschr., 1908, xxxiv, 2262.

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and Graham¹ confirm these observations and believe that by taking into account the degree of tuberculin hypersensitiveness of the tested individual as evidenced by the minimal cutaneous reaction, more uniform results are obtained. A weak point in Pickert and Löwenstein's contention is that they failed utterly to neutralize the activity of tuberculin injected subcutaneously into guinea pigs, and we must look upon the whole question as an open one, since such an experienced investigator as Römer could not confirm the results in animals.²

We may sum up the objections to the Wassermann-Bruck view of the tuberculin reaction:

1. It fails to account for the local reactions.
2. It would seem that tuberculin hypersensitiveness may occur in the absence of a tuberculous focus.
3. It is difficult to understand how tuberculin and anti-tuberculin can exist independently side by side in a tuberculous focus if they possess such a strong affinity for one another.
4. Morgenroth points out that complement acts only on the combination to which it is bound and could not, as Wassermann and Bruck assume, cause necrosis of tuberculous tissue.
5. The results of the practical application of the test are too conflicting to allow any satisfactory deduction about the conditions under which the reaction occurs and its specificity.

Hertwig,³ in the year that tuberculin was introduced, advanced an ingenious physical theory to account for its action. It has been shown that malic acid exerts a marked

¹ White and Graham: Studies on the action of sera on the tuberculin cutaneous reaction. *Jour. Med. Research*, 1909, xvi, 261.

² Römer: Beitrag zum Wesen der Tuberkulose Immunität-Antikörperstudien. *Beitr. z. Klin. d. Tuberk.*, 1910, xxii, 372.

³ Hertwig: Ueber die physikalische Grundlage der Tuberkulinwirkung, 1891, cit. Wolff-Eisner.

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chemotactic action upon the spermatozoa of ferns and that the degree of attraction can be varied by accustoming the spermatozoa to different strengths of the acid. Hertwig assumes that tuberculin exerts a negative chemotactic action upon the leukocytes, but that repeated injections so change this relation that the concentration of tuberculin at the focus of infection comes to strongly attract them, and by drawing them in great number about the diseased area secures its localization. If tuberculin be injected in large amounts, the tuberculin concentration in the serum comes to exceed that in the focus of disease, the leukocytes are drawn thence into the blood stream, with them come tubercle bacilli and the disease is likely to spread.

That tuberculin is without toxic action in healthy individuals, and that a certain incubation period is necessary before its effects become manifest in the tuberculous, has led to the belief that either tuberculin is the mother substance from which the toxic material is prepared or else that it stimulates certain cells to produce this substance. What an important place the former alternative has in the most recent views upon tuberculin activity we shall soon point out. Marmorek is the most notable champion of the second. Marmorek¹ contends that tuberculin is not the reaction-producing substance of the tubercle bacillus, but that the true toxin is richly secreted by the bacilli under its influence. This true toxin he believes to have artificially obtained by growing tubercle bacilli under unusual conditions which he considers similar to those surrounding their growth in the animal body. By injecting it into horses he has attempted the preparation of an antituberculous serum which has been extensively used in treatment. As a sup-

¹ Marmorek: Antituberculose-Serum und Vaccin. Berl. klin. Wehnschr., 1903, xl, 1108; Beitrag zur Kenntnis der Virulenz der Tuberkelbacillen. Ibid., 1906, xliii, 328; Weitere Untersuchungen über den Tuberkel-bacillus und das Antituberkuloseserum. Ibid., 1907, xliv, 621.

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port to his view he claims that one can produce a characteristic reaction by injecting tuberculin immediately following the introduction of tubercle bacilli, a contention that no other investigator has succeeded in confirming.

We come finally to a consideration of those views which now command the widest attention, and as they depend so completely upon theories that have only recently been elaborated, we shall digress to note the observations upon which the theories of anaphylaxis rest.¹

As early as 1839 Magendi² observed that rabbits who had received, without displaying any unusual symptoms, an injection of egg white were killed when, after a lapse of several days, a second injection was given. Curiously this very remarkable result did not attract special comment and until quite recently the frequent and unexpected death of experimental animals following the repeated injection of foreign proteid to produce precipitins, or for other purposes, failed to arrest an inquisitive attention. Arloing in 1888 found that repeated injection of microorganisms, instead of producing immunity, caused the animals to succumb more quickly upon subsequent reinfection. He expressed the opinion that microorganisms secrete a soluble toxin that breaks down the natural defensive resources of the body. Arloing thus realized that one infection may

¹ For more comprehensive consideration of the literature upon the subject consult:

Besredka: *Über anaphylaxie*. Kraus u. Levaditi: *Handbuch der Technik und Methodik der Immunitätsforschung*. Erster Ergänzungsband, Jena, 1911, 209.

Beidl and Kraus: *Die experimentelle Analyse der anaphylaktischen Vergiftung*. Ibid., 255.

v. Pirquet: *Allergy*. Arch. Int. Med., 1911, vii, 259.

Anderson and Rosenau: *Anaphylaxis*. Ibid., 1909, iii, 519.

Doerr: *Die Anaphylaxie*. Kraus u. Levaditi: *Handbuch der Technik u. Methodik der Immunitätsforschung*, Jena, 1909, ii, 856.

Otto: *Anaphylaxie und Serumkrankheit*. Kolle and Wassermann: *Handbuch der pathogenen Mikroorganismen*, 1908, Ergänzungsband ii, 255.

² Magendi: Cit. v. Pirquet, loc. cit.

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completely change the relation of the animal toward subsequent reinfection. At his suggestion his pupil Courmont repeated the experiments with tubercle bacilli.¹

Flexner² in 1894 noted that animals who had withstood a single injection of dog's serum were, after a lapse of some days or weeks, killed by its repetition.

Richet and Hericourt³ in 1898 found that injections of eel serum, instead of immunizing dogs, rendered them more sensitive to its action and that repeated injections caused death. Somewhat earlier than this, in 1895, Brieger⁴ made the interesting observation that a goat whose serum and milk contained large amounts of antitoxin nevertheless died of typical tetanus. Knorr⁵ in the same year published his investigations of this phenomenon upon laboratory animals in which he demonstrates that guinea pigs immunized to diphtheria and tetanus antitoxin acquire a markedly increased sensitiveness. Salomonsen and Madsen⁶ likewise noted that horses immunized to diphtheria toxin were affected by doses of the toxin, which the amount of antitoxin in their blood should easily have neutralized and Kretz⁷ was able to show that normal animals failed to react to toxin-antitoxin mixtures which produced evident symptoms in immunized animals. v. Behring and Kitashima⁸ review the whole question and add the instance of

¹ Courmont: *Étude sur les substances solubles prédisposant à l'action pathogène de leurs microbes producteurs*. Rev. de méd., 1891, xi, 843.

² Flexner, cit. Lewis: Further observations on anaphylaxis to horse serum. Jour. exper. Med., 1908, x, 608.

³ Richet and Hericourt, cit. Doerr, loc. cit., p. 35.

⁴ Brieger: Weitere Erfahrungen über Bakteriengifte. Ztschr. f. Hyg. u. Infektionskrankh., 1895, xix, 101.

⁵ Knorr: Experimentelle Untersuchungen über die Grenzen der Heilungsmöglichkeit des Tetanus. Habilitationsschrift, Marburg, 1895.

⁶ Salomonsen and Madsen: Recherches sur la marche de l'immunisation active contre la diphtérie. Ann. de l'Inst. Pasteur, 1897, xi, 315.

⁷ Kretz, cit. Doerr, loc. cit., p. 35.

⁸ v. Behring and Kitashima: Ueber Verminderung und Steigerung der erbten Giftempfindlichkeit. Berl. klin. Wehnschr., 1901, xxxvii, 157.

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a horse highly immunized to diphtheria toxin who still succumbed to an injection of the toxin. They name this remarkable phenomenon the paradoxical reaction and speak of the condition as hypersensitiveness.

In spite of these numerous isolated and suggestive observations, it is only just to acknowledge that the recognition of their importance and the principle of their general applicability dates from the thorough investigations of Richet. Richet and Portier,¹ working with a highly poisonous proteid body, obtained from a sea anemone, actinia, found that 0.2 gram per kilo, administered intravenously, is fatal to dogs. Following an injection of 0.1 gram the animals show only transient symptoms of indisposition, but, if the same dose be repeated after an interval of several weeks, they immediately develop marked dyspnea, vomiting and diarrhea and die within an hour. Richet regarded this action as directly opposed to immunity, for the animals are rendered by it more vulnerable and in this spirit named it anaphylaxis, the absence of protection. In subsequent contributions he tells how by purification he was able to obtain a far more potent protein which he calls "Congestin," because the anatomical lesions following death from its administration consist chiefly in an intense hyperemia of, with hemorrhage into, the walls of the digestive tract. Richet established certain definite principles regarding the anaphylactic action of the substance which future work has confirmed for other proteins.

1. The necessity of a definite time interval between the sensitizing and the toxic dose.

2. The duration of the anaphylactic condition, lasting often for seven weeks.

3. The rapid appearance of the anaphylactic symptoms and, if death does not occur, their slow retrogression.

¹Richet and Portier: De l'action anaphylactique des certains venins. *Compt. rend. soc. de biol.*, 1902, liv, 170.

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4. The independence, within certain limits, of the hypersensitiveness from the size of the original dose.

5. That the anaphylactic action of actinia was in some way bound to the proteid constituent.

That Richet must have had the last point strongly fixed upon his attention, and that he must have surmised that the principles enunciated for actinia poisoning would apply equally well to other proteid intoxications, is evident from the work he instigated Arthus to undertake. Arthus¹ showed that rabbits are unaffected by subcutaneous, intraperitoneal or by intravenous injections of horse serum unless they have been sensitized by a previous injection. Such sensitized animals subsequently display marked infiltration about the site of subcutaneous injections and are profoundly affected by even small amounts of the serum introduced directly into the circulation. Following an intravenous injection of 2 cm. of serum, guinea pigs immediately become anxious and restless, lie upon the belly and pant with great rapidity, the respirations reaching 200 and 250; there is discharge of feces and the animals, falling on their sides with head drawn back, make active running movements, and after a few deep breaths are dead. The whole reaction occupies but a few minutes. Arthus further demonstrated that guinea pigs can be sensitized to milk, in which case the anaphylactic shock is liberated by subsequent injections of milk. Animals sensitized to milk are not susceptible to horse serum and vice versa, from which observation he concludes the anaphylactic phenomenon is strictly specific and can be liberated only by the special proteid to which the animal has been rendered hypersensitive.

Simultaneously with the work of Arthus and quite independent of it, appeared the invaluable clinical observations

¹ Arthus: Injections répétées de sérum de cheval chez le lapin. *Compt. rend. soc. de biol.*, 1903, p. 817.

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of v. Pirquet and Schick.¹ These authors, studying the symptoms following serum injections, which they designate the serum sickness, noted that in children receiving the first dose such symptoms, when they develop, occur after an incubation period of from eight to ten days, whereas a second injection may be followed almost immediately by urticaria, edema, nausea and collapse. In a certain number of cases this, what v. Pirquet and Schick call the "immediate reaction," fails to appear and similar but usually milder symptoms occur on the fifth or sixth day, the "accelerated reaction." Indeed, exceptionally both reactions occur in the same individual. In a subsequent study of revaccination, the same authors made similar observations, showing that upon primary vaccination the pustule appears on the fourth day, while upon subsequent revaccination a mild reaction occurs within twenty-four hours and rapidly subsides. This change in the reactivity of the organism occasioned by an injection of foreign protein v. Pirquet designates "Allergy," and emphasizes especially the altered time reaction. He has fully considered the importance of the immediate reaction in the diagnosis of previous contact with a foreign protein. Their studies have thrown a flood of light upon our ideas of the incubation period in infection.

In 1904, during Ehrlich's visit to America, his attention was called by Theobald Smith to the observation that guinea pigs, used for testing the potency of diphtheria antitoxin, became acutely sick and frequently died following an injection of normal horse serum given a few weeks later. Upon his return to Germany Ehrlich set Otto to work out the details of the problem. Otto² showed conclu-

¹ v Pirquet and Schick: *Zur Theorie der Inkubationszeit*. Wien. klin. Wehnschr., 1903, xvi, 1244; *Die Serumkrankheit*, Leipsic, 1905.

² Otto: *Das Theobald Smith'sche Phänomen der Serumueberempfindlichkeit*. v. Leuthold Gedenkschrift, 1905, i.

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sively that neither toxin nor antitoxin plays a part in the production of the hypersensitiveness, but that the serum itself is the active factor. In all details the Theobald Smith reaction is identical with the phenomenon of Arthus, both being characterized by the anaphylactic shock and, as Lewis¹ particularly has shown, after non-fatal subcutaneous doses by extensive local reactions about the site of injection.

In 1906 appeared the first of a number of notable contributions by Rosenau and Anderson.² Stimulated by an investigation of the fatalities following the administration of diphtheria antitoxin, they proceeded to study the effects of toxin, antitoxin and normal serum upon animals. They fully substantiate the previous work of Arthus and Otto and add many valuable details.

Because the phenomenon of anaphylaxis is a recent addition to our knowledge and its mechanism but little understood, as well as on account of its profound significance for a consideration of the tuberculin reaction and tuberculosis immunity, we have been led to thus sketch its development. From this point on, however, the contributions become too numerous to note more than a few of the important ones. They have served chiefly to strengthen the fundamental observations upon which the new principle rests and to fill out important gaps in our knowledge of its details. It will suffice for our purpose to review briefly the conclusions which have followed from the work.

All protein bodies, whether primarily toxic or not, have the remarkable property of stimulating in the animal organism a reaction that renders a subsequent injection highly

¹ Lewis: The induced susceptibility of the guinea pig to the toxic action of the blood serum of the horse. *Jour. Exper. Med.*, 1908, x, 1.

² Rosenau and Anderson: A study of the cause of sudden death following the injection of horse serum. *Bull. No. 29, Hyg. Lab., U. S. P. H. and M. H. S.*, 1906.

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poisonous. A certain lapse of time is necessary after the original injection before the acquired sensitiveness is manifested. This time interval is not sharply limited, the sensitiveness appearing on the sixth day, or even earlier, and progressively increasing over a period of some weeks.¹ Rosenau and Anderson² determine the average period of incubation to be about 10 days. Hypersensitiveness is best induced by parenteral introduction, but it has been claimed to follow the feeding of foreign proteins. The sensitiveness is specific for the substance which has stimulated it. An animal anaphylactic to horse serum will show no reaction to egg albumen. The same animal may be rendered sensitive to several different proteins by injecting them separately or simultaneously. Anaphylaxis is transmitted by the mother to the offspring,³ although not equally to all the young of the same litter.⁴ Very small amounts of protein may produce anaphylaxis, in one instance only 0.000,001 c. c. of horse serum exciting sensitiveness.⁵ The anaphylactic shock followed by death may be liberated by 0.1 c. c. serum intraperitoneally, by 0.25 c. c. injected into the brain and by 0.01 c. c. given directly into the heart. The addition of disinfectants and various chemicals which do not destroy the protein is without influence upon its sensitizing power. Besredka⁶ claimed that serum heated to 70° C. for one hour still retains its toxic power but its potency is decreased at higher temperature and at 100° C. is

¹ Lewis: The induced susceptibility of the guinea pig to the toxic action of the blood serum of the horse. *Jour. Exper. Med.*, 1908, x, 1.

² Rosenau and Anderson: The specific nature of anaphylaxis. *Jour. Infect. Dis.*, 1907, iv, 552.

³ Rosenau and Anderson: Simultaneous transmission of resistance to diphtheria toxin and hypersusceptibility to horse serum by the female guinea pig to her young. *Jour. Med. Research*, 1906, x, 259.

⁴ Lewis: *Loc. cit.*

⁵ Anderson and Rosenau: Anaphylaxis. *Arch. Int. Med.*, 1909, iii, 519.

⁶ Besredka: Comment peut-on combattre l'anaphylaxie? *Ann. de l'Inst. Pasteur*, 1907, xxi, 950.

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completely lost. However, the sensitizing power is retained and even 120° C. does not completely destroy it. When hypersensitiveness has become established it may remain for a long time. Anderson and Rosenau allowed a period of 732 days to elapse between the two injections and express the belief that the acquired anaphylaxis to horse serum may continue during the lifetime of the guinea pig. Currie¹ obtained a definite reaction in a man 187 days after the first injection of horse serum.

Otto² and, later, Rosenau and Anderson³ noted that guinea pigs displaying marked anaphylactic symptoms after a test injection but recovering showed upon subsequent injection only slight or no symptoms. Rosenau and Anderson speak of this as immunity. The question was studied in detail by Besredka and Steinhardt,⁴ who call the acquired resistance "Antianaphylaxis." The sensitiveness developed by the administration of serum may be restrained by injecting a large dose or repeated small doses of the serum during the period of incubation. After the anaphylaxis has become fully developed intraperitoneal injections afford an easy means of obliterating it. A highly sensitized animal may, after a single large but non-fatal dose, be rendered completely refractory in two hours. The same result is obtained, and without producing any symptoms, by injecting smaller and increasing doses intraperitoneally. Otto found the antianaphylaxis produced by single doses to be but temporary; on the fourth day sensitiveness had returned. Besredka and Steinhardt, inducing it by re-

¹ Currie: Examples of the immediate and of the accelerated reaction following two injections of antidiphtheria serum. *Jour. Hyg.*, 1907, vii, 61.

² Otto: Das Theobald Smith'sche Phänomen der Serumueberempfindlichkeit. v. Leuthold Gedenkschrift, 1905, i.

³ Anderson and Rosenau: Anaphylaxis. *Arch. Int. Med.*, 1909, iii, 519.

⁴ Besredka and Steinhardt: Du mecanisme de l'anti-anaphylaxie. *Ann. de l'Inst. Pasteur*, 1907, xxi, 384.

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peated injections, found their guinea pigs still completely immune at the end of three months.

Otto made the very important observation that the anaphylactic condition may be passively transferred to a normal animal by administering the serum of an actively sensitized animal. From this work, which has been fully substantiated by numerous investigators, five significant facts have come:

1. The anaphylaxis is not transferred immediately. It requires about 24 hours for the animal to become sensitive.

2. The anaphylaxis can be transferred during the period of incubation, showing that the sensitizing substance [anaphylactic reaction bodies (Otto); Sensibilisin (Besredka); Toxogenine (Richet); Allergin (v. Pirquet); Albuminolysin (Nicolle); Anaphylactin (Gay)] is present in the blood before the animal itself has developed hypersusceptibility.

3. The serum of sensitive animals, rendered antianaphylactic and thus refractory, can still passively convey sensitiveness to normal animals. Thus the sensitizing body, the anaphylactin, is neither destroyed nor neutralized in the process of immunization.

4. Anaphylactin rapidly disappears from the blood of actively sensitized animals and passive transference becomes impossible long before the animals themselves lose their hypersensitiveness.

5. Sensitized females rendered antianaphylactic still transmit hypersusceptibility to their young.

The experimental data so far at hand do not permit of a single convincing interpretation of the phenomenon of anaphylaxis and indeed numerous views are sustained upon the nature of its mechanism.¹ To v. Pirquet and Schick we owe the first attempt to bring it directly into relation with other processes of immunization, an attempt to ex-

¹ See particularly Otto, loc. cit., p. 42.

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plain its development as an active response on the part of the organism in protecting itself against foreign proteid material by an exuberant elaboration of antibodies. It is difficult to concede at first sight that a process rendering reinfection so commonly and promptly fatal should be viewed as a protective mechanism. Indeed, the name it bears shows how deeply Richet, its sponsor, felt that it was anything but protective, for he calls it anaphylaxis, the opposite of prophylaxis. It is quite possible, however, that such a mechanism, protective under some conditions, may under others, when over-developed or brought abnormally into play, exhibit disadvantageous features. It is this view which is now generally maintained. Vaughan considers the name anaphylaxis an extremely unfortunate one, because animals succumbing to serum anaphylaxis die, to his way of thinking, of over-protection and in this particular instance of useless protection. However, if the foreign protein introduced into the organism happens to be endowed with life, our interpretation of the mechanism immediately changes. The protein grows and flourishes unhindered until certain reactive processes set up in the body elaborate substances which are viewed as protective and have been extensively studied under the names, agglutinins, precipitins, lysins, opsonins. To these we must now add those processes of which hypersensitiveness is the manifestation. The exact manner in which the response causing anaphylaxis works is debatable but, as we shall later show, evidence is in favor of the view that concomitantly with its development the organism does somehow acquire the ability to restrict the growth of infecting bacteria and indeed it would seem that upon its development the immunity to certain diseases depends.

This by no means compels the conclusion that hypersensitiveness itself is a desirable condition. It is possible that it is an unfortunate accompaniment of an otherwise

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invaluable process. v. Pirquet, Vaughan,¹ Wolff-Eisner,² Richet,³ and numerous others consider the anaphylactic phenomenon to be due to a splitting of the protein molecule, one of the decomposition products being highly toxic. If this view be true the ultimate aim of the process is to split up and destroy foreign protein and that one of the products formed in reaching this end should prove deleterious might be but incidental. Fever and the other constitutional symptoms attending an infection have come to be viewed generally as an anaphylactic expression. They are a necessary part of the organisms' reactivity, but whether in themselves beneficial is as yet an unanswerable question.

As we have said, the sensitizing substance present in the serum of actively anaphylactized animals is regarded by most observers as an antibody resulting from a stimulation of the animal's cells. There are, however, notable differences from this view. Gay and Southard⁴ look upon anaphylactin as an element of normal horse serum which is retained in the circulation and acts as an irritant upon the body cells, stimulating them to assimilate rapidly certain other elements of horse serum. For these authors the whole reaction is played in the cells and is not due to an antigen-antibody combination in the serum. They believe their histological studies support this view. Rosenau and Anderson contest the specificity of the hemorrhages they describe, noting them commonly in other conditions, and

¹ Vaughan and Wheeler: The effects of egg white and its split products on animals; a study of susceptibility and immunity. *Jour. Infect. Dis.*, 1907, iv, 476.

² Wolff-Eisner. *Frühdiagnose und Tuberkulose Immunität*, 2nd edition. Würzburg, 1909.

³ Richet: De la substance anaphylactisante ou toxogénine. *Comp. rend. soc. de biol.*, 1908, lxiv, 846.

⁴ Gay and Southard: On the mechanism of serum anaphylaxis and intoxication in the guinea pig. *Jour. Med. Research*, 1908, xviii, 407.

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were unable to find the fatty changes described by Gay and Southard in many regions.

Although the conception of the presence of an antibody as an integral part in the explanation of anaphylaxis has become general, there is division of opinion upon the question of the unity of the sensitizing and toxic substances. Rosenau and Anderson, v. Pirquet, Otto, Nicolle and others believe that the same portion of the proteid that sensitizes on the first injection is responsible for the toxic symptoms following the second. Vaughan has been able to split proteins into alcohol-soluble and alcohol-insoluble portions, which are respectively poisonous and non-poisonous. The poisonous or toxophore portion he considers common to all proteins and the substance that produces the anaphylactic symptoms. The non-poisonous or haptophore portion sensitizes animals by the production of a specific proteolytic ferment which splits the injected protein, thus liberating the toxophore portion. The characteristic symptoms are due to the marked avidity of certain cells in the central nervous system, notably cells in the respiratory center, for this poisonous portion.

Besredka¹ still more clearly enunciates a dual hypothesis. He names the sensitizing substance sensibilisinogen, the reaction or immune body sensibilisin, and the symptom-producing substance antisensibilisin. The sensibilisin is stored in the nerve cells. It possesses a keen attraction for the antisensibilisin normally present in horse serum and the sudden union of the two in the nerve cells produces the anaphylactic symptoms. If antisensibilisin is introduced when sensibilisin is present in small amount, as during the incubation period, or if sensitiveness be fully developed and small amounts of antisensibilisin be introduced, the combination occurs more slowly, the nerve cells are gradu-

¹ Besredka: Du mecanisme de l'anaphylaxie vis-à-vis du sérum de cheval. Ann. de l'Inst. Pasteur, 1908, xxii, 496.

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ally desensibilisinized and mutual neutralization or anti-anaphylaxis occurs. Besredka was able to give strong support to the contention that the anaphylactic shock takes place in the nerve cells by showing that ether prevents the development of symptoms, although antianaphylaxis follows as in unetherized animals. The weak point in Besredka's hypothesis is that *in vitro* sensibilisin will not unite either with its antigen, sensibilisinogen, or with antisensibilisin, for normal serum mixed with the serum of anaphylactic animals will still produce the anaphylactic shock in sensitive animals, and will induce both active and passive hypersusceptibility in normal animals.

Besredka, to further support the view of separate sensitizing and poisonous portions in serum, advances experiments showing that, while sensibilisinogen is highly thermostable, resisting temperatures of 120° C., antisensibilisin is partially destroyed at 70° C. Rosenau and Anderson were unable to confirm these results. Important support comes from the work of Gay and Adler.¹ By purifying horse serum with ether and precipitating fractionally with ammonium sulphate, they find that, as the ammonium sulphate concentration increases, fractions are obtained of decreasing sensitizing power and increasing toxicity. The last fraction is as toxic as normal horse serum, but far less sensitizing than serum of the previous fractions. The first fraction, which they call euglobulin and consider identical with anaphylactin, is as potent to sensitize as normal horse serum, but absolutely devoid of toxic properties.

Friedberger² has, in an interesting way, attempted to identify the toxic substance producing anaphylactic shock

¹ Gay and Adler: The chemical separation of the sensitizing fraction (anaphylactin) from horse serum. Jour. Med. Research, 1908, xviii, 433.

² Friedberger: Die anaphylaxie mit besonderer Berücksichtigung ihrer Bedeutung für Infektion und Immunität. Deutsch. med. Wehnschr., 1911, xxvii, 481.

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with precipitin. By activating precipitin with complement he obtains a mixture, anaphylatoxin, which is toxic for normal animals, liberating, according to Friedberger, the characteristic symptoms of anaphylaxis. Biedl and Kraus,¹ in an effort to repeat Friedberger's work, admit obtaining a toxic substance by the addition of complement to precipitin, but claim that the symptoms it produces are distinctly different from those characteristic of true anaphylaxis. Among the many authors who have tested the validity of Friedberger's results the view is general that while toxic effects may occasionally be obtained they are strikingly inconstant. To explain this inconstancy Friedberger makes an ingenious suggestion which necessitates some preliminary considerations in order to be clear. As we have said, it is generally conceded that the anaphylactic reaction body, whose presence is assumed, exercises enzymotic properties. Nothing could be more striking than the almost absolute identity of the symptoms of anaphylaxis and those of peptone poisoning. The assumption at once presents itself that the specific enzyme partially splits up the proteid molecule, forming peptones which produce the hypersensitive symptoms. The objection has been made that such small quantities of protein are necessary to induce the anaphylactic shock that hardly enough peptone would be formed. Not to make matters too complicated we merely mention that one investigator has sought to derive the toxic substance from the specific antibody. Allowing that peptone is the poisonous substance we could easily imagine that if but little lysin be present the transformation goes on so slowly that no intoxication occurs, or indeed if lysin be present in large amount the decomposition of the proteid molecule may occur so rapidly that as soon as peptones

¹ Biedl and Kraus: Die experimentelle Analyse der Anaphylaktie Vergiftung. Kraus u. Levaditi: Handbuch der Technik und Methodik der Immunitätsforschung. Erster Ergänzungsbund, Jena, 1911, p. 255.

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are formed they are split at once into simpler non-toxic polypeptids, or into the component amino acids. This, Friedberger contends, is at the bottom of the failures to repeat his experiments. The precipitin-complement mixture must be incubated just the proper length of time for peptones to be present and further splitting avoided.

The physiological mechanism of anaphylaxis depends on a toxic action upon smooth muscle. Auer and Lewis¹ have shown that death in guinea pigs is due to asphyxia occasioned by tetanic contraction of the smooth muscle of the bronchioles. Animals succumb even when the vagus is sectioned, which demonstrated that the action is peripheral and must be either upon the muscle cells directly or on the vagus endings.² Schultz³ has found that portions of the intestinal wall from sensitized animals show a more decided irritability to contact with horse serum than similar portions from unsensitized animals.

We have until now spoken of anaphylaxis as a condition following the administration of serum. We have said that this very remarkable sensitizing property is common to all proteins, but, as the fundamental experiments have been made with horse serum, perhaps the general applicability of the phenomenon has not been sufficiently emphasized. We wish now to lay this emphasis and, what is more directly to our purpose, to add that all of the principles developed for horse serum apply equally as clearly to bacterial proteid.⁴ Extracts of typhoid, colon, hay, cholera,

¹ Auer and Lewis: The physiology of the immediate reaction of anaphylaxis in the guinea pig. *Jour. Exper. Med.*, 1910, xii, 151.

² Auer: The effects of resection of one vagus upon serum anaphylaxis in guinea pigs. *Proc. Soc. Exper. Biol. and Med.*, 1910, vii, 103.

³ Schultz: *Physiological Studies in Anaphylaxis*. I. The reaction of smooth muscle of the guinea pig sensitized with horse serum. *Jour. Pharm. and Therap.*, 1909, i, 549.

⁴ Wolff-Eisner: *Ueber Eweissimmunität und ihre Beziehungen zur Serum*

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anthrax, etc., bacilli sensitize to subsequent injections and the sensitiveness is specific. The anaphylaxis may be passively transferred from a sensitive to a normal animal, as in horse serum experiments.

Before speaking of the application of the principles of anaphylaxis to an interpretation of the tuberculin reaction, it is advisable to consider what tuberculin is. Bacteriologists have long distinguished two different poisonous substances obtained from bacteria: 1. The exotoxins or toxins secreted by the organisms and present in the culture media and 2. The endotoxins or toxins intimately associated with the living protoplasm of the bacteria and liberated only upon their disintegration.

The exotoxins are probably a product of bacterial metabolism and their distinguishing features are their primary toxicity and the readiness with which they stimulate in the animal organism the production of neutralizing bodies called antitoxin.

Endotoxins are intimately bound up with the living protoplasm of bacteria and are liberated when the organisms are disintegrated by certain ferment or lytic substances within the body. Although antitoxins have been obtained to endotoxins, their appearance is exceptional and in general it is correct to say they produce no antitoxin.

While we shall not here give the details of preparation of the innumerable tuberculins that have been used, we may say in general that they consist of the culture fluid in which tubercle bacilli have grown, of ground-up tubercle bacilli or extracts of their bodies, and of both combined. On the basis of the immunity principles established for other diseases it has been customary until recently to speak of

krankheit. Centrabl f. Bakteriologie, 1906, xl., 378; Rosenau and Anderson; loc. cit., p. 41.

Krause and Doerr: Über Bakterienanaphylaxie. Wien. klin. Wchnschr., 1908, xxi, 1008.

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the antitoxic-producing properties of the filtrates and the anti-bacterial-stimulating properties of the bacillary bodies. It is Wolff-Eisner¹ who has most clearly shown that there is in fact no ground to sustain such a distinction. Tuberculins, whether from the filtrate or bacillary body, always produce essentially the same effects, there being differences in the degree but never in the character of the reaction. Indeed they act as living tubercle bacilli do save that they are devoid of the power of growth and reproduction. Wolff-Eisner has worked with tuberculin which microscopically was shown to contain numerous acid-fast tubercle bacilli particles. Passed through a Chamberland or Berkefeld filter, the filtrate is found free from such particles and still it produces reactions identical with, although weaker than, those of the original unfiltered product. There has never been adduced any convincing evidence that such filtrates produce antitoxins, while they do, on the other hand, regularly stimulate hypersensitiveness in the tuberculous, according to the principles of protein anaphylaxis. Until contradictory evidence is forthcoming, if such evidence ever can be obtained, the conclusion is completely justified that all tuberculins, if active, owe their activity to the presence of the specific protein of the tubercle bacillus, whether this be in solution, in ultramicroscopic particles, in microscopic particles or in unaltered bacillary bodies. It is interesting to note the absolute failure attending efforts, such as Maragliano's and Marmorek's, to produce antitoxic sera to tuberculous disease.

The source of the tubercle bacilli from which the tuberculin is prepared is of the greatest importance. It has been generally known that different strains of tubercle bacilli produce widely varying tuberculins. The variation, however, is in the strength alone, the character of their efforts

¹ Wolff-Eisner: Frühdiagnose und Tuberkuloseimmunität. Würzburg, 1909, 228.

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being invariably the same. So much has been claimed for difference in diagnostic and therapeutic effect between tuberculin from human and tuberculin from bovine tubercle bacilli that it is of the greatest importance to emphasize that this statement applies with equal justice to products from these two sources. Römer,¹ after an extensive investigation of the effects of tuberculin from human, bovine and fowl tubercle bacilli upon animals (guinea pigs, cattle, chickens and rabbits) infected with human, bovine and fowl tubercle bacilli, concludes that there is no essential difference in the character of the effects the three produce. Indeed human and bovine tuberculin are so identical in their action upon infected animals that we may neglect to ascertain their source. These results are fully sustained in a recent publication of Weber and Dieterlen.² These authors test the effect of human and bovine tuberculin upon tuberculous cattle and upon guinea pigs infected with human and bovine bacilli. While they find that even marked differences in potency may exist in tuberculin from different sources, the quality of the reaction is always the same.

THE TUBERCULIN REACTION INTERPRETED AS A HYPERSENSITIVE PHENOMENON

The earliest investigators of the phenomenon of anaphylaxis, notably v. Pirquet and Richet, were at once struck with the evident similarity between the tuberculin reaction and protein hypersensitiveness and point to the tuberculin reaction as the clinical manifestation most clearly paralleling the experimental results. There are some minor diffi-

¹ Römer: Tuberkulose u. Tuberkulinreaktion. Beitr. z. Klin. d. Tuberk., 1910, xvii, 428.

² Weber and Dieterlen: Vergleichende Untersuchungen über die Tuberkuline aus Menschen und Rindertuberkelbazillen. Tuberkulosearbeiten aus dem Kaiserl. Gesundheitsamte, 1910, No. 10, pp. 1-100.

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culties in the way of an exact superimposing of the phenomena but in general these early impressions have gained in force and distinctness. The excellent clinical observations of Löwenstein and Rappaport¹ are the first to clearly emphasize the interpretation of the tuberculin reaction as an evidence of hypersensitiveness. Koch had previously noted that, when following a diagnostic injection there is a slight reaction, by repeating the same dose a more decided reaction is usually liberated. This has become a guiding precept in conducting the subcutaneous tuberculin test. Its explanation has been generally sought² in the assumption of a summation of doses. Löwenstein and Rappaport show that a typical reaction may follow the third, fourth or fifth administration of the same dose of tuberculin which failed to produce a reaction after the first and second injection. That such increasing sensitiveness is not due to summation they clearly establish by demonstrating that the acquired hypersusceptibility may persist for a year. They conclude that the conditions are analogous to the hypersusceptibility studied by v. Behring³ in animals immunized to diphtheria toxin. One of us⁴ has further demonstrated that reactions may occur to descending doses.

Wolff-Eisner⁵ has more clearly and in greater detail than any other author applied the principles of anaphylaxis to an explanation of the tuberculin reaction. We can see nothing essentially different in Wolff-Eisner's explanation from that of v. Pirquet, Vaughan and others, although he insists upon its individuality. The chief distinction is that

¹ Löwenstein and Rappaport: Ueber den Mechanismus der Tuberkulinimmunität. Ztschr. f. Tuberk., 1904, v, p. 485.

² Vide Bandelier, loc. cit., p. 18.

³ v. Behring: Cited p. 36.

⁴ Hamman: The use and value of tuberculin in the diagnosis of pulmonary tuberculosis. Arch. Int. Med., 1908, i, 443.

⁵ Wolff-Eisner: Frühdiagnose und Tuberkulose Immunität. 2nd edition, Würzburg, 1909, p. 243.

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he speaks of the reaction body specifically as lysin, while others call it generically an antibody and ascribe to it fermentative properties. Wolff-Eisner's hypothesis is briefly this: Consequent upon the stimulation of a tuberculous infection the animal organism elaborates abundantly specific lysins. These lysins attack and rapidly disintegrate tubercle bacillus proteid that may subsequently gain entrance into the body. The endotoxins thus set free act as poisons when the cells of the body are in a receptive or hypersensitive state. This hypersensitive state is supposed to depend upon sessile receptors. In normal individuals no, or only very small, amounts of lysin are present; therefore not enough endotoxin is liberated and the reaction does not occur.

Sahli¹ gives warm support to Wolff-Eisner's view, showing how it fits better than other explanations into what is at present known about the action of tuberculin. He is, however, unable to see the necessity of assuming the presence of a cellular hypersensitiveness. To him the presence of lysins is the only factor of importance, for if endotoxins are liberated it is superfluous to further require a peculiar predisposition of the cells to their influence. In other words, the presence of sufficient lysin constitutes hypersensitiveness.

We grant that hypothetically Sahli is quite right but a knowledge of the studies of the mechanism of anaphylaxis, especially the results of Gay and of Auer and Lewis, and of the principles underlying the passive transference of sensitiveness will not permit so simple an explanation, for they indicate clearly the important part played by the cells in the occurrence of the reaction. We may mention too the results of Manwaring,² who washed out the blood

Sahli: *Tuberkulinbehandlung*, 3 aufl., Basel, 1910.

Manwaring: The physiological mechanism of anaphylactic shock. *Johns Hopkins Hosp. Bull.*, 1910, xxi, 275.

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of sensitized animals with the blood of normal animals and found that they retained their hypersensitiveness, but the hypersensitiveness could no longer be passively transmitted to normal animals. That antianaphylactin does not depend alone upon changes in the blood is indicated by the fact that horse serum mixed with the blood of refractory animals does not lose its power to liberate the anaphylactic shock in sensitive animals. After considering in great detail the satisfactory features of the lytic theory, Sahli naively proceeds to say that should subsequent investigation prove the assumption unwarranted he has an almost equally satisfactory histogenic theory to offer in advance.

There are two features of tuberculin hypersensitiveness that are not in accord with the principles of serum anaphylaxis:¹

1. In normal animals tuberculin injected in large or small amounts, at long or short intervals, never gives rise to hypersensitiveness.

2. Attempts at passive transference of tuberculin hypersensitiveness have not been uniformly successful.

We have shown how readily tuberculin increases a sensitiveness that is present in the individual and this fact has led to erroneous interpretations. For instance Vaughan² instilled tuberculin into the conjunctival sac of 110 healthy students. Six reacted. Twenty-one days later a second installation was made into the same conjunctival sac and 59

¹ Since this was written these difficulties have been cleared up. Dr. C. R. Austrian, working in the Laboratory of the Phipps Dispensary of the Johns Hopkins Hospital, has succeeded beyond question in sensitizing guinea pigs with the blood of a tuberculous individual to subsequent post-orbital injections of tubercle bacillus proteid. The patient was extremely sensitive to tuberculin. The experiments fulfill all the demands of characteristic passive transference of sensitiveness. That tuberculin does not occasion sensitiveness in healthy animals probably depends upon the very small amount of tubercle bacillus proteid in tuberculin.

² Vaughan: Discussion on tuberculin. Jour. Am. Med. Assn., 1909, lii, 34

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per cent. reacted, some violently. Rosenau and Anderson¹ instilled a drop of a 1 per cent. solution of tuberculin into the conjunctival sac of 12 healthy men and none reacted. After fifty-one days a second instillation of the same strength, or in a few cases of a weaker solution, was made and ten reacted definitely. These authors conclude that an application of tuberculin to the mucous membrane of a normal individual causes local sensitiveness to subsequent contact. The work of Hamburger upon children proves conclusively that repeated subcutaneous injections arouse no hypersusceptibility and in the new born repeated conjunctival instillations likewise never produce a reaction. In healthy individuals reacting to repeated tuberculin applications there must be a latent sensitiveness acquired from a previous infection that is aroused. Calmette obtained positive conjunctival reactions in rabbits by injecting small doses of tuberculin sixteen hours before the application. Wolff-Eisner could not confirm these results. We have been ourselves unable to sensitize the conjunctivæ of rabbits by injections of large or small amounts of tuberculin, or by repeated instillations in the same eye. Hamill, Carpenter and Cope² and Nobécourt and Mantoux³ have further negatived Calmette's contention by demonstrating that the conjunctivæ of rabbits cannot be uniformly sensitized even after the animals have acquired tuberculosis. Römer⁴ has satisfactorily proved that tuberculosis-free cattle can never be sensitized by subcutaneous or intra-

¹ Rosenau and Anderson: The ocular reaction to tuberculin: a warning. *Jour. Am. Med. Assn.*, 1908, 1, 961.

² Hamill, Carpenter and Cope: A comparison of the v. Pirquet, Calmette and Moro tuberculin tests and their diagnostic value. *Arch. Int. Med.*, 1908, ii, 405.

³ Nobécourt and Mantoux, cit. Villaret et Tixier: Le diagnostic de la tuberculose par les méthodes d'investigation recentes et en particulier par les réactions à la tuberculin. *Rev. de la Tuberc.*, 1908, Series 2, v. 355.

⁴ Römer: Tuberculose u. Tuberkulinreaktion. *Beitr. z. Klin. d. Tuberk.*, 1910, xvii, 430.

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venous injections of tuberculin. Baldwin¹ obtained equally negative results in guinea pigs. This inability of tuberculin to sensitize normal animals does not invalidate the application of the fundamental principles of serum hypersensitiveness to the tuberculin reaction, for working with pure tubercle bacillus protein Baldwin and Krause² have reproduced nearly all of the important phenomena observed with horse serum. The size of the dose and the manner of application are crucial factors. On account of their far-reaching significance we quote Baldwin's conclusions:³

1. A true anaphylactic sensitization can be produced in guinea pigs by the pure protein substance of the tubercle bacillus extracted by water at 50° C.

2. Intradural toxic injections through the optic foramen produce all the symptoms of fatal anaphylactic shock with respiratory stimulation and paralysis. Intravenous toxic injections are also effective but less typical symptoms follow, while intraperitoneal injections are practically negative in result.

3. A single injection of tuberculo-protein equal to 0.000,8 gram dry weight is sufficient to sensitize a normal guinea pig; probably even less is required.

4. Tuberculous animals are sensitive but not uniformly so to acute anaphylaxis tests. There is no absolute relation between the degree of sensitiveness and the stage of the disease. As a rule it is lost in the far-advanced stage. Repeated inoculation increases it.

5. Acute anaphylaxis could not be demonstrated in the offspring of inoculated guinea pigs, but is very uniformly

¹ Baldwin: Hypersusceptibility to tuberculin in tuberculosis. *Yale Med. Jour.*, 1909, xv, 266.

² Krause: Hypersensitiveness to tuberculo-protein and its relation to some tuberculosis problems. *Jour. Med. Research*, 1911, xxiv, 361.

³ Baldwin: Studies in immunity to tuberculosis. Hypersusceptibility or anaphylaxis. *Jour. Med. Research*, 1910, xxii, 189.

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produced in those of sensitized mothers injected during pregnancy. This transmitted sensitiveness is very marked. It is not demonstrated whether it is actively produced in the fetus or passively conveyed through the placental blood.

6. Sensitized guinea pigs which survive a toxic injection become refractory to a subsequent one for a time or at least react less strongly. The temperature is not regularly elevated or depressed after toxic injection.

7. Sensitization is possible with both the filtered bacillary extract and the washed residue (T. R.).

8. Toxic injections are more effective with an unfiltered centrifugalized extract than with the filtrate. Old tuberculin was uncertain.

9. Bovine bacillary extract is very toxic to guinea pigs sensitized to human bacillary extract, but the latter was not toxic to animals sensitized to *B. Timotheus* extract; that is, human and bovine protein act reciprocally, but the timothy bacillus protein does not.

10. Sensitized normal guinea pigs do not react to ordinary tuberculin like tuberculous guinea pigs, yet some respond slightly to an intradermic test. This difference between anaphylactic sensitization and tuberculin reactivity need not be fundamental, as it is possibly due to another factor as yet undetermined.

11. Transferred or passive anaphylaxis was unsuccessful from tuberculous guinea pigs to sound ones; also from rabbit to rabbit and from rabbit to guinea pig. From human to guinea pig the results were uncertain but to rabbit partially successful.

Krause has further shown that intraperitoneal toxic injections are effective, although the symptoms are delayed and progress much more slowly than following intradural injections. "The resulting intoxication will tend to approximate what is generally observed as the tuberculin reaction in the infected guinea pig." A boiled glycerin

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extract of tubercle bacilli prepared to imitate original tuberculin both sensitized and produced toxic symptoms. Original tuberculin itself liberates anaphylactic symptoms when injected post-orbitally into sensitive animals.

Up to the present unquestionable passive transference of tuberculo-protein hypersensitiveness has not been accomplished. Yamanouchi¹ was able, by injecting the serum of tuberculous patients intraperitoneally into young rabbits, to kill the rabbits from 24 to 48 hours later by the intravenous administration of tuberculin. We will not detail the technical objections raised by Joseph² to Yamanouchi's work. Joseph himself obtained only negative results by using the intracutaneous test and looking for a local reaction as the index of tuberculin hypersensitiveness. Krause,³ in an effort to repeat Yamanouchi's experiments, has shown that young rabbits are extremely sensitive to intravenous injections of tubercle bacillus extract and that the symptoms so produced are indistinguishable clinically from those of anaphylaxis.

We have discussed serum anaphylaxis at some length and no doubt gave the impression that, applied to a consideration of the tuberculin reaction, it would illuminate this heretofore dark field, but in making the application we have disappointingly spoken of much disagreement. Since it corresponds with the state of our knowledge we do not regret the undecided and somewhat bewildered frame of mind the whole discussion has created. In its broad principles tuberculin hypersensitiveness unquestionably is closely related to the phenomenon of protein hypersensitiveness. The time of its development after infection, the character

¹ Yamanouchi: Ueber die Anwendung der Anaphylaxie zu diagnostischen Zwecken. Wien. klin. Wchnschr., 1908, xxi, 1623.

² Joseph: Zur theorie der Tuberkulin überempfindlichkeit. Beitr. z. Klin. d. Tuberk., 1910, xvii, 461.

³ Krause: Studies in passive or transferred anaphylaxis. Jour. Med. Research, 1910, xxii, 257.

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of the reaction symptoms, its elevation following the administration of small amounts of tuberculin, all are significant points. Baldwin and Römer have shown that tuberculin hypersensitiveness develops in from 7 to 15 days after infection by tubercle bacilli. The passive transference of sensitiveness demanded as the crucial test of its existence has been but questionably successful. Still the results of Baldwin's experiments indicate that at least partial transference is possible and perhaps, after all, the difference is only relative and not fundamental.

It is possible to kill guinea pigs by repeated injections of tuberculin. The animals do not present symptoms resembling anaphylaxis or tuberculin hypersensitiveness, but at autopsy show the intense congestion of organs constantly found after death from protein anaphylaxis. Finally, it has been objected by Doerr and Joseph that death following the injection of tuberculin into tuberculous guinea pigs is clinically a far different phenomenon from fatal anaphylactic shock. Baldwin and Krause, however, have shown that animals sensitized by tubercle bacillus extracts are affected by tuberculin injected intradurally and some show a suggestive intracutaneous tuberculin reaction. Are the two, protein hypersensitiveness and tuberculin hypersensitiveness, varying expressions of the same fundamental principle or is a different mechanism behind each? We accept with Baldwin the first alternative and believe a more thorough understanding of protein hypersensitiveness will in the end clear away the numerous difficulties in the path of a satisfactory explanation of the tuberculin reaction.

Krause¹ has made an interesting suggestion which, although purely hypothetical, we mention on account of its ingeniousness. He assumes that perhaps hypersensitiveness to the tubercle bacillus is only one feature of tubercu-

¹ Krause: Experimental studies on tuberculo-protein hypersensitiveness and their possible applications. Johns Hopkins Hosp. Bull., 1911, xxii, 250.

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losis infection. The animal body may concomitantly be sensitized to the products of degeneration arising in the tuberculous focus. The inflammatory focal reaction following an injection of tuberculin may throw unusually large amounts of these products into the circulation and the animal may respond hypersensitively to them. The fever and other constitutional symptoms would thus be a secondary anaphylactic reaction.

TUBERCULIN INSENSITIVENESS

A lack of reaction to tuberculin may occur under a number of conditions.

1. Uninfected Individuals.—We have spoken sufficiently of the specificity of the tuberculin reaction to make it unnecessary to repeat that a reaction to tuberculin always indicates an infected individual. Infection, however, does not always produce the same degree of hypersensitiveness and very large doses would be required to exclude infection definitely. The local reactions are far more sensitive than constitutional reactions to ten milligrams, which is the usual high dose in diagnostic injections, and give results more closely in accord with anatomical findings.

2. Healed Tuberculous Lesions.—Patients who have clinically recovered from a tuberculous lesion display a wide variation in tuberculin hypersensitiveness. Some lose it completely, in many it is maintained indefinitely at a high level and in others all possible gradations occur. It has been frequently suggested that the tuberculin test is the most decisive means of proving that complete healing has taken place. While there are a number of facts that may be used as arguments to favor this view, the test cannot be employed clinically as a satisfactory guide. Anatomically it may have such a significance. We know that the hypersensitiveness occasioned by the introduction of

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virulent or feebly virulent organisms which leave no permanent lesion is but temporary, disappearing after seven or eight months. Cattle rendered immune by injections of human tubercle bacilli show such a passing hypersensitiveness. This leads one to believe that permanent hypersensitiveness is due to continuous absorption from a tuberculous focus. Therefore it may be that in spite of clinical and even anatomical evidence of healing when hypersensitiveness has persisted some leakage from the lesion has continued to occur. We have shown that the tuberculin test is more delicate evidence of infection than the results of an anatomical examination and perhaps, too, loss of hypersensitiveness is the most refined indication we possess of absolute healing.

3. Acute Tuberculous Infections.—At least in man acute tuberculous infections with severe constitutional symptoms frequently occur with absent tuberculin hypersensitiveness. Therefore even the local tuberculin tests are notoriously fallacious in miliary tuberculosis. No doubt in most instances, had the patients been previously observed, the absent reaction would have been found due to the obliteration of a previously well-marked hypersensitiveness. There is no rule in the matter, for not infrequently hypersensitiveness is present and remains throughout the illness.

4. During the Period of Incubation.—Animal experiments have established that a period of from 7 to 15 days must elapse after infection before tuberculin hypersensitiveness develops.

5. During Infectious Diseases.—v. Pirquet¹ has shown that tuberculin hypersensitiveness disappears during an attack of measles to reappear during convalescence. Grüner²

¹ v. Pirquet: Das Verhalten der kutanen Tuberkulinreaktion während der Masern. Deutsch. med. Wehnschr., 1908, xxxiv, 1297.

² Grüner: Ueber die Herabsetzung der Tuberkulinempfindlichkeit Tuberkulöser während der Masern. München. med. Wehnschr., 1909, lvi, 1681.

has demonstrated, however, that the loss is not complete. It has been suggested that this loss of reactivity may account for the frequency with which active tuberculosis develops during or immediately after an attack of measles. Hamburger¹ has noted a similar diminution of sensitiveness in pneumonia, diphtheria, scarlet fever and cerebrospinal meningitis, although other observers have been unable to confirm these observations. Indeed Klein and John² have found that scarlet fever may revive a fading cutaneous reaction and many have claimed that conjunctival reactions are unusually common during convalescence from typhoid fever.

6. Advanced Stages of Tuberculous Disease.—Especially in advanced pulmonary tuberculosis is the reactivity to tuberculin frequently diminished or completely lost. We are not in a position to give an account of the mechanism by which the tuberculin hypersensitiveness is curtailed, but it does in some way seem to be related to an exhaustion of the reacting power of the body. We gladly admit that this is a restatement of our ignorance in another form. Koch himself ascribed the loss of reacting power to a saturation of the body cells with large amounts of tuberculin from the diseased focus. This view has been widely accepted but has no experimental basis. At least it has been impossible to demonstrate the presence of tuberculin in the blood of patients with advanced pulmonary disease.³

7. Unexplained Conditions.—There are instances of definite tuberculous lesions, not advanced, which have failed to produce sensitiveness in an individual otherwise in good condition. We can give no satisfactory explanation for

¹ Hamburger, cit. v. Pirquet.

² Klein and John: Das Wiederaufflammen einer bereits abgelaufenen Hautreaktion während einer Scharlachinfektion. Wien. med. Wchnschr., 1908, lvii, 1831.

³ Wolff-Eisner: Frühdiagnose und Tuberkulose immunität. 2nd edition, Würzburg, 1909, p. 272.

these exceptions, which are extremely rare and enter but slightly as a disturbing factor in practical application. They are usually small lesions, well cut off from the general circulation.

8. Tuberculin Treatment.—In most instances, by administering gradually increasing doses of tuberculin, it is possible to completely obliterate tuberculin hypersensitivity. Why in some cases this is impossible and how, when successful, the change is brought about are questions which are shrouded in the uncertainty enveloping explanations of the details of the tuberculin reaction. Tuberculin immunity, as this refractory condition following treatment is called, is broadly analogous to the antianaphylaxis to horse serum and is developed in much the same manner. We have previously noted that the serum of animals rendered antianaphylactic may still passively transmit hypersensitivity to other animals, indicating that the antibody (lysin, ferment), whose presence is assumed in most theories proposed to explain the condition, is not neutralized. We must then either assume the development of a second antibody to neutralize the toxic principle liberated by the disintegration of tuberculin, or look upon cellular changes as determining the condition. It has been already pointed out how important histogenic changes are in an interpretation of the data at hand concerning the hypersensitive condition, and the paradoxical reaction to diphtheria toxin lends itself as a ready comparison to the conditions in tuberculin immunity. Wolff-Eisner¹ believes that notably the connective tissue develops receptors that bind the liberated endotoxin and thus prevent it reaching the cells of important centers in the nervous system. It is well known that, following an injection of tuberculin, points where tuberculin has previously been applied, either subcutane-

¹ Wolff-Eisner: Zur Kutan- und Konjunktivalreaktion. Beitr. z. Kl. d. Tuberk., 1909, xii, 155.

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ously or upon the skin or mucous membranes, display a tendency to flare up. Such local reactions are frequently marked when focal and general reactions are absent, which Wolff-Eisner interprets as a binding of the endotoxin at these points, thus preventing it from reaching the focus of disease and the nervous centers. Again not infrequently such local reactions are marked where the constitutional reaction occurs, but is mild and delayed. This he interprets as a not completely successful effort on the part of the connective tissue areas to withhold the endotoxin, some becoming free and causing mild focal and general reactions.

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The clinical experience that tuberculosis confers no appreciable protection against subsequent development of the disease, that relapse, indeed, is the rule rather than an exception, had prevailed in firmly establishing the view that no immunity is developed by tuberculosis, until this conviction was shaken by the investigations of the past few years. These investigations rest upon the fundamental observation of Koch on the difference in behavior of normal animals and those already infected with tuberculosis toward cutaneous inoculation of tubercle bacilli. This observation has realized a significance in the light shed by modern ideas of immunity which could not have been assumed for it at the time it was made. Subsequent investigations have, however, only modified the conditions of the experiment and enlarged its application. We now know that tuberculosis confers an immunity as genuine and as easily demonstrable as do most infectious diseases and that the protection is not at first sight apparent depends upon the nature of the disease.

An animal infected with tuberculosis rapidly acquires an altered power of reaction toward subsequent injections

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of tubercle bacilli. This altered reactivity is exhibited in different ways, depending upon the manner and the intensity of the reinfection.

1. If a large number of tubercle bacilli are injected the animal dies in a few hours with symptoms of a profound intoxication.

2. If the dose be small there is a prompt reaction about the site of injection which destroys the tubercle bacilli and prevents infection even of the regional lymph glands.

3. If the size of the dose be larger than that which the animal is able to resist, but not large enough to liberate acute fatal intoxication, infection does occur but the resulting lesions are chronic and slowly progressing as compared with those produced by the same dose in normal controls.

The animal with tuberculosis can then successfully resist reinoculation of tubercle bacilli in quantities surely fatal for normal animals, although the same mechanism which protects it under these conditions is destructive when the number of bacilli is very large. The acute death following large doses has been studied in detail by Bail,¹ the immunity to small doses most thoroughly by Römer.² As a graphic illustration of the difference in the reaction to the introduction of tubercle bacilli of normal and of tuberculous animals, and of tuberculous animals to small and to large doses, we reproduce Chart XIV of Römer and Joseph.

The control healthy sheep receives intravenously, on November 22, 1 mg. per 10 kg. of body weight of virulent tubercle bacilli. The temperature does not begin to rise until the 25th and reaches its maximum on December 2.

¹ Bail: Der akute Tod von Meerschweinchen an Tuberkulose. Wien. klin. Wchnschr., 1905, xviii, 211; Ueber das Aggressin des Tuberkelbazillus, *ibid.*, 547; Ueber Giftwirkung von Tuberkelbazillen beim Meerschweinchen, *ibid.*, 1212.

² Römer and Joseph: Die tuberkulöse Reinfektion. Beitr. z. Klin. d. Tuberk., 1910, xvii, 287.

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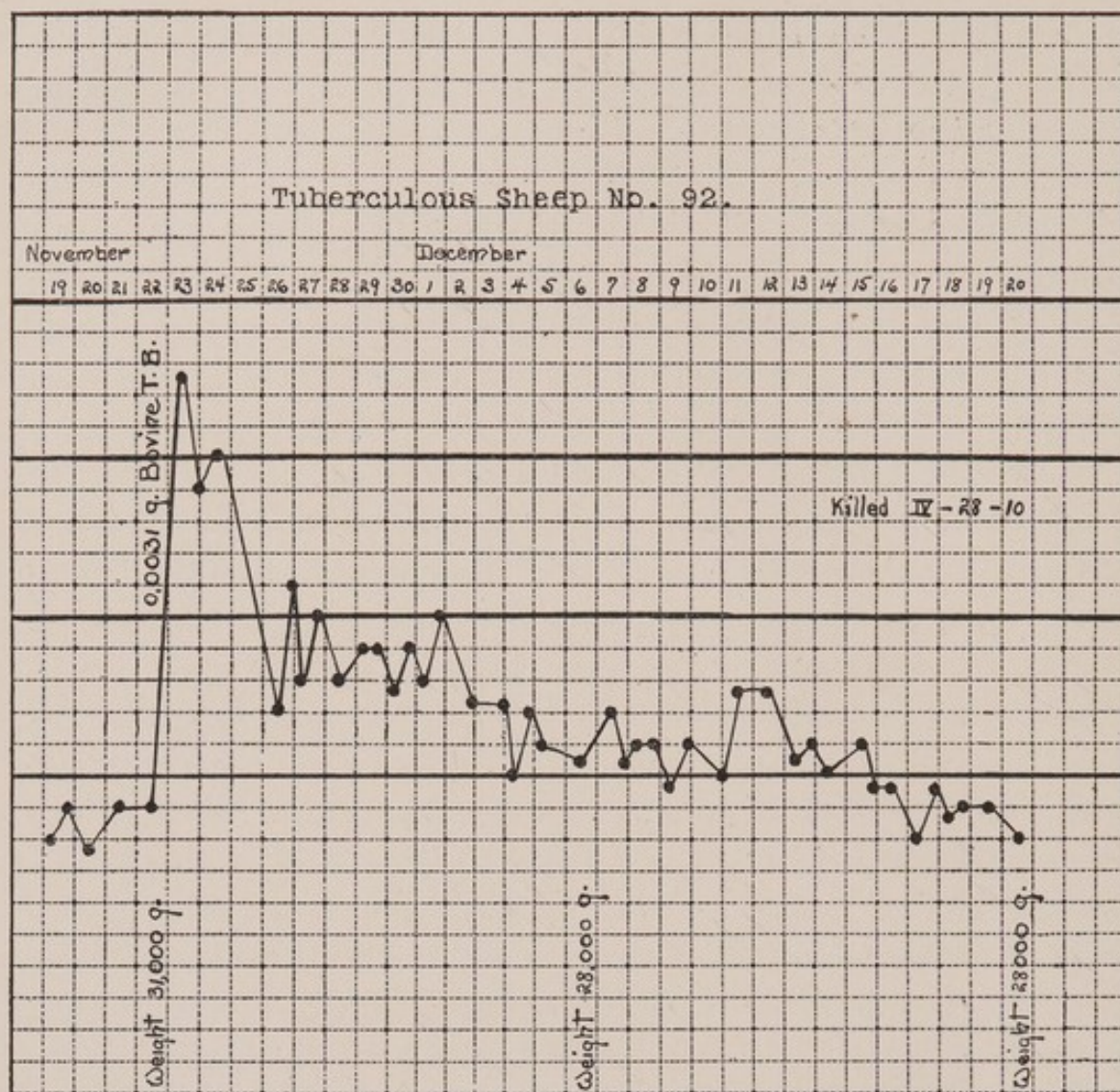


FIG. IIA.—CHART ILLUSTRATING THE EFFECTS OF THE INJECTION OF SMALL AND LARGE DOSES OF TUBERCLE BACILLI IN TUBERCULOUS AND NON-TUBERCULOUS SHEEP. (After Römer and Joseph.)

The animal then rapidly succumbs to a severe infection, dying on December 20, having lost greatly in weight.

The tuberculous sheep No. 71 was infected on August 6, 1908, with one-tenth mg. per 10 kg. body weight of virulent tubercle bacilli and on January 4, 1909, with two-thirds mg. per 10 kg. of body weight. Reinfection on November 22, with one mg. per 10 kg. body weight, is followed by an intense immediate reaction and death within forty-eight hours. At autopsy there is a large subcutaneous infiltra-

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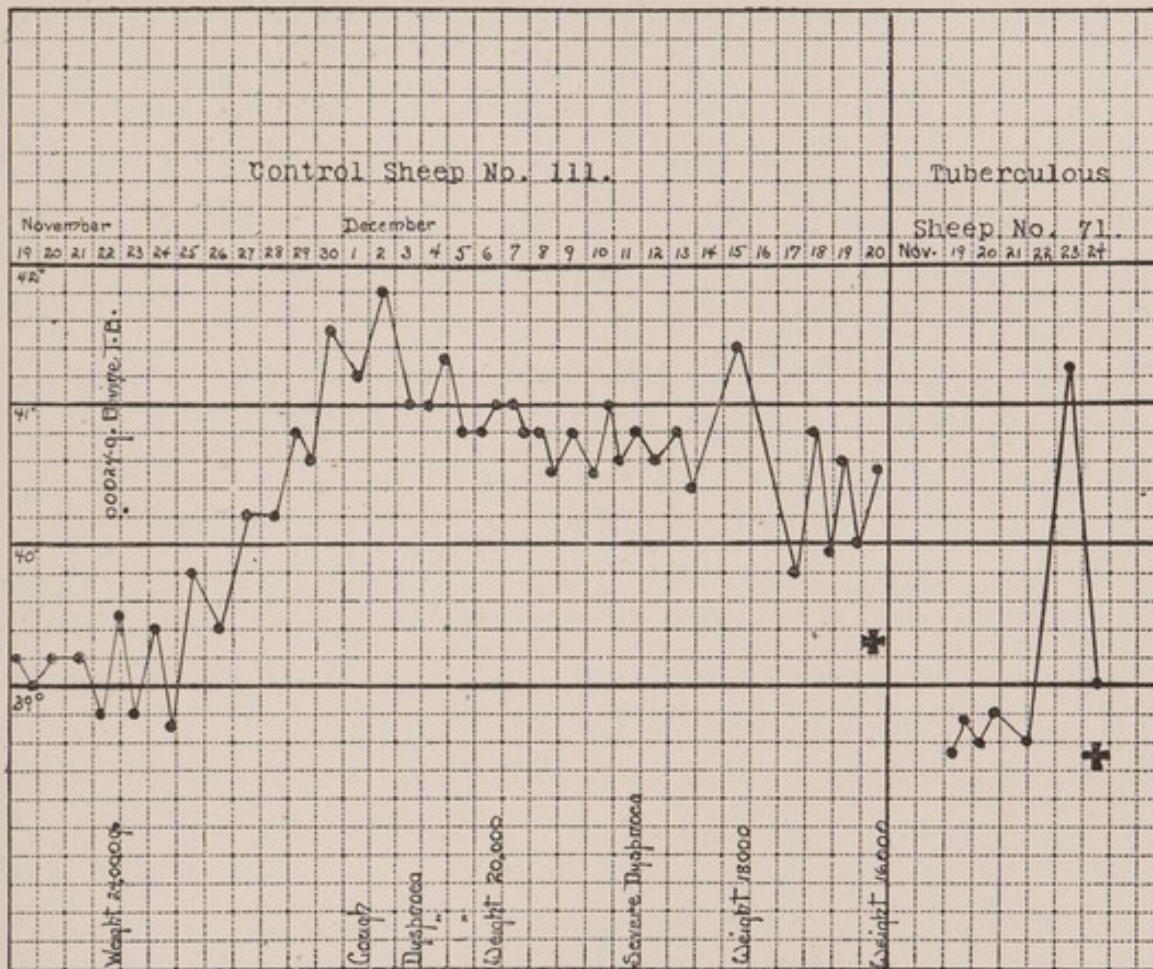


FIG. IIb.—CHART ILLUSTRATING THE EFFECTS OF THE INJECTION OF SMALL AND LARGE DOSES OF TUBERCLE BACILLI IN TUBERCULOUS AND NON-TUBERCULOUS SHEEP. (After Römer and Joseph.)

tion at site of first inoculation, no infiltration at point of second inoculation.

The tuberculous sheep No. 92 was infected January 4, 1909, with eight-tenths mg. per 10 kg. of body weight, and reinfected November 28, 1909, with one mg. per 10 kg. body weight. This is followed by a prompt and intense reaction which, however, gradually subsides, and the animal returns to its previous condition of good health. Killed on April 28, 1910, the animal shows at autopsy diffuse tuberculous lesions throughout the glands, liver and lungs. These lesions are the remains of the primary infection in January, 1909, for a control sheep inoculated at the same time and

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in the same manner, but not reinoculated, displayed almost identical lesions.

A dose of tubercle bacilli producing in a healthy animal a rapidly fatal infection in one tuberculous animal causes immediate death; in a second tuberculous animal, causes symptoms of intense intoxication promptly and, when these subside, the animal rapidly recovers and suffers no permanent damage from the infection.

These results, so contradictory at first sight, are easily reconcilable. It is reasonably probable that the mechanism, whatever it may be, which causes the immediate toxic reaction on reinfection is the same upon which the animal withstanding this reaction depends for its complete protection. How analogous these phenomena are to the general principles of anaphylaxis, as previously outlined, is at once apparent. The animals have by one infection been rendered hypersensitive to subsequent contact. This hypersensitiveness is, as we have shown, a valuable protective asset but if the reinfecting dose be large the animal succumbs with the symptoms of an acute intoxication.

The immunity afforded by an infection with tubercle bacilli follows only upon the introduction of a virulent organism. Allied acid-fast bacilli and avirulent tubercle bacilli produce but slight if any protection. The attempts that have been made in this direction are too numerous to allow more than a few to be noted as examples. Led on by the observation that the serum of goats and asses immunized to tubercle bacilli agglutinates not only tubercle bacilli but likewise a number of other acid-fast organisms, and that animals previously treated with, for instance, the timothy bacillus agglutinated these and tubercle bacilli as well, Koch¹ employed timothy bacillus and an organism cultivated from the glowworm in attempts to develop im-

¹ Koch, Schütz, Neufeld, Miessner: Ueber die Immunisirung von Rindern gegen Tuberculose. Ztschr. f. Hyg. u. Infectiouskrankh., 1905, li, 300.

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munity. The protection produced was, however, so slight and so transient that the method was abandoned. Similar acid-fast bacilli used on guinea pigs and rabbits produce at best but a retarding influence upon the development of the disease. Levys¹ in numerous experiments has employed tubercle bacilli whose virulence has been decreased in various ways and has claimed some immunity to follow their use. Römer, in going over Levys' work, gets the impression that definite results have been obtained only when the injected organism is still virulent for the animal. In the same manner he discards the work of Bartel,² who claims to have obtained some protection by using tubercle bacilli rendered avirulent by prolonged contact with glandular substance. Calmette, Guérin and Breton³ obtained no satisfactory results with glycerin-treated cultures.

The experiments of Trudeau are particularly enlightening in this connection.⁴ He found that animals inoculated with living but attenuated human tubercle bacilli show a much higher grade of immunity than those inoculated with bacilli killed by heat and with piscian tubercle bacilli. Of two strains of human tubercle bacilli, the more virulent gave the greater protection. As Trudeau comments, the immunity does seem to be the outcome of the struggle between the bacilli and the tissues. Histological examination of the organs of the animals experimented upon gave results of special interest. The vaccinated animals showed, upon inoculation, an early and violent reaction about the bacilli,

¹ Levys, cit. Römer: *Tuberkulosevaccine*. Kraus and Levaditi: *Handbuch d. Technik u. Methodik der Immunitätsforschung*. Ergänzungsband, 1911, i, 337.

² Ibid., 338.

³ Calmette, Guérin and Breton: *Contribution à l'étude de la tuberculose expérimentale du Cobaye*. Infection et essais de vaccination par la voie digestive. *Ann. de l'Inst. Pasteur*, 1907, xxi, 401.

⁴ Trudeau: Two experiments in artificial immunity against tuberculosis. *Med. News*, 1905, lxxxvii, 633.

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followed by their disintegration and subsequent absorption of the exudate. In controls there is no initial inflammatory change, the bacilli settling unopposed in the organs, tubercles slowly forming and then going on to caseation.¹ Römer,² too, states firmly that satisfactory protection is only developed in the presence of living virulent tubercle bacilli.

Upon these principles rests the successful preventive inoculation of cattle as practiced by v. Behring and Koch. In this procedure hypersensitiveness is developed in the absence of a tuberculous focus. When a tuberculous lesion exists the protection lasts either until the focus heals or the animal's defense is broken down by advancing disease, while the protection afforded cattle by the injection of human tubercle bacilli is but temporary, disappearing in from 12 to 18 months.

How complete the immunity is following the inoculation of calves with human tubercle bacilli may be seen, for example, from Koch's experiments.

The method he finally used was this: A large number of cultures were made from human tuberculous lesions, by inoculating guinea pigs with the material and obtaining a pure culture from the spleen. The organisms were grown on glycerin agar and glycerin bouillon and were from 4 to 6 weeks old before being used. The organisms were then carefully dried on filter paper, the dried material carefully weighed and then rubbed with sterile salt solution in an agate mortar. Injections were made in the jugular vein. On the first injection some of the calves received 1 cg., others 2 cg. of tuberculin; on the second injection all received 5 cg. An interval of from 1 to 2 months sepa-

¹ Nichols: An histological study of the lesions of immunized rabbits. Tr. Nat. Assn. for the Study and Prev. of Tuberc., 1905, i, 149.

² See Römer: Tuberkulosevaccine. Kraus and Levaditi: Handbuch d. Technik u. Methodik der Immunitätsforschung. Ergänzungsband, 1911, i, 310.

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rated the two. Eighteen calves were selected, which did not react to tuberculin. After the first injection there was a rise of temperature, which lasted several days and then subsided, although in some there was slight elevation for weeks after. The animals usually lost weight but after several weeks rapidly recovered. None of them appeared very ill after the injection. The second inoculation was given when all the effects of the first had completely subsided—in from 4 to 6 weeks—after which there was a slight elevation of temperature but no disturbance of the general health. The test injections consisted of 2 cg. of bovine tubercle bacilli from a strain which was frequently controlled and caused death in normal animals in from 20-30 days. The first calves received their injection about 40 days after the second protective inoculation, the others 12 months after. Of the first six calves Nos. 1 and 5 showed no tuberculosis, No. 2 pulmonary tuberculosis and Nos. 3 and 4 serous membrane and renal tuberculosis, and No. 6 generalized tuberculosis. Calves 1, 3 and 5 had received 2 cg. as the initial protective dose, calves 2, 4 and 6, 1 cg. Of the calves which had received 2 cg., 2 remained free from tuberculosis and one showed only slight lesions in the serous membranes and a few tuberculous areas in the kidney, while, of the 3 which had received only 1 cg., one died in 30 days of general tuberculosis, one killed on the 165th day showed widespread disease of the lungs and one showed only slight disease of the serous membranes and kidneys. Therefore the animals receiving 2 cg. showed a richer and more rapid production of protective substances.

Of the second group of 12 calves tested after 3 months Nos. 8, 9, 12, 14 and 17 showed absolutely no tuberculosis, 13 and 15 showed small healed areas of tuberculosis; these 7 calves were killed over a year after the injection of the fatal dose of bovine tubercle bacilli, the other 5, which

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had remained perfectly healthy and showed no evidence of tuberculosis, were allowed to live for further experimentation. This series brings out very prominently the advantage of a delay in administering the fatal dose after giving the second protective inoculation. Tubercle bacilli from various human sources having been used shows also that the immunizing property does not reside in any special strain of bacilli. A calf was treated in a similar manner to the above with attenuated bovine cultures. Killed after the test inoculation, it showed no tuberculosis.

Three other calves were inoculated with a single dose of human tubercle bacilli of 1, 2 and 3 cg., respectively. After 103 days they received the usual fatal dose of bovine tubercle bacilli, but remained perfectly healthy and when killed, in from 117-127 days later, showed absolutely no tuberculosis.

Two calves treated with a single injection of attenuated bovine tubercle bacilli likewise were rendered immune. One of these is still alive and healthy, one killed showed at autopsy villous pleuritis, bronchitis and peribronchitis (not tuberculous).

It is important to emphasize that, while tuberculosis confers marked immunity to tuberculous infection, the original lesion may, and usually does, continue to progress. Attempts to produce resistance to the disease already established by the injection of a small number of virulent bacilli or of organisms attenuated by various means have not been accompanied by striking success. Undoubtedly, however, the immunity that is developed plays an important part in the prevention of a generalization of the disease and we have come to look to it as an explanation of many of the characteristic features of tuberculous infection. For the organism is protected not only against invasion from without but also against metastases from within. Römer has shown that tuberculous guinea pigs are equally resistant

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to reinfection with bacilli cultivated from their own lesions as to those derived from other sources.

Webb and Williams,¹ using the ingenious method of Barber for isolating single bacilli, have, by injecting a single living tubercle bacillus and gradually raising the number, finally succeeded in administering many times the fatal dose to guinea pigs and monkeys.

These facts, which have been learned experimentally, about tuberculosis have had a profound influence upon our ideas of infection and the disease in man. Studies in tuberculin hypersensitiveness and the clinical course of the disease are fruitfully interpreted in their light. Their truth has been tested upon guinea pigs, rabbits, cattle, sheep, goats and monkeys, and their complete applicability to man cannot be doubted.² That an individual infected with tuberculosis has a marked resistance to reinfection, both from within and without, is abundantly attested. In no other way can we explain the relative infrequency of involvement of the larynx, tonsils and cervical lymph glands and intestines and mesenteric glands in advanced pulmonary tuberculosis, for innumerable bacilli passing through and lodging upon these tracts offer abundant opportunity for infection. Particularly the work of Liebermeister,³ Treupel⁴ and Jessen and Rabinowitsch⁵ have shown how commonly tubercle bacilli gain entrance to the blood stream

¹ Webb and Williams: Immunity in tuberculosis. *Jour. Med. Research*, 1911, xxiv, 1; *Am. Jour. Med. Asso.*, 1911, lvii, 1431.

² Römer: Tuberkulose-Immunität und Phthiseogenese. *Beitr. z. Klin. d. Tuberk.*, 1910, xvii, 411.

³ Liebermeister: Studien über Komplikation der Lungentuberkulose und über die Verbreitung der Tuberkelbazillen in der Organen und im Blut der Phthisiker. *Virchows Arch.*, 1909, clxvii, 332.

⁴ Treupel: Die Bedeutung des Tuberkelbazillennachweises im strömenden Blute. *München. med. Wehnschr.*, 1909, lvi, 2195.

⁵ Jessen and Rabinowitsch: Ueber das Vorkommen von Tuberkelbazillen im kreisenden Blute und die praktische Bedeutung dieser Erscheinung. *Deutsch. med. Wehnschr.*, 1910, xxxvi, 1116.

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and how seldom their lodgment in organs in small number produces lesions. Hamburger in this connection has pointed out that individuals harboring mild tuberculous lesions are never successfully reinfected by contact with patients suffering from severe disease, even under conditions leading to close association. Particularly the statistics from English hospitals show how seldom physicians and attendants upon consumptives developed the disease even in the period antedating the discovery of the tubercle bacillus and the application of the preventive measures still more recently introduced. It has been a matter of constant comment how rarely persons affected with tuberculosis of the skin develop pulmonary lesions and when this complication does occur how benign the disease is.

As in animals so in man this immunity is only relative. There is evidence that under many conditions its power varies and while it successfully protects against mild reinfection it cannot completely resist a more intense one. Even when reinfection establishes a new focus of disease, however, the course of events is largely modified and in this altered behavior toward infection we see the cause of the varied clinical course of tuberculous disease in infected and uninfected individuals.

It has long been remarked clinically how differently tuberculous disease is manifested in children and in adults. In children lesions of the glands, bones, serous membranes, skin and generalized tuberculosis are the usual types of the disease, while chronic pulmonary tuberculosis, the predominant form in adults, is but rarely found. v. Behring¹ was the first to suggest a satisfactory explanation of this singular difference. He found that it was impossible to produce pulmonary phthisis in guinea pigs with a single injection of tubercle bacilli, but that repeated injections fre-

¹ v. Behring: Tuberculoseentstehung, Tuberculosebekämpfung und Säuglingsernährung. Beiträge zur experimentellen Therapie, Heft 8, Berlin, 1904.

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quently cause characteristic chronic lesions of the lungs. From these experimental results von Behring drew parallel conclusions for man, announcing that pulmonary tuberculosis could develop only in a previously infected individual. With keen insight he placed the date of infection in early childhood and, although recent work has not sustained his view of the mode and source of infection, the tuberculin reactions particularly have fully confirmed his contention of the age at which infection occurs. These views have been extended notably by Römer, to whose work we have so frequently referred. Neufeld¹ in goats and Weber and Titzes² in cattle have likewise shown that in immunized animals injections of tubercle bacilli large enough to overcome the resistance produce chronic forms of the disease, such as never occur after a single injection. Many authors have drawn an interesting comparison between tuberculosis and syphilis. The primary lesion with infection of the regional lymph glands, the secondary phenomena represented in tuberculosis by the skin, bone and serous membrane lesions, and the late or tertiary symptoms by pulmonary phthisis. Hamburger, in an interesting monograph,³ has ably elaborated these views.

The immunity that follows tuberculin infection is as potent against reinfection from within as from without. The spread of the disease is certainly accomplished by recurring reinfection which in most instances is what Römer calls a metastatic autoinfection. Such reinfection is, however, quite different in its results from a primary infection and follows the principles learned from experimental reinfection in animals.

¹ Neufeld: Über Immunisirung gegen Tuberkulose. Deutsch. med. Wehnschr., 1903, xxix, 653.

² Weber and Titzes: Immunisirung der Rinder gegen Tuberkulose. Tuberkulosearbeiten aus dem kaiserl. Reichsgesundheitsamte, Hefte 7, 9 and 10.

³ Hamburger: Kindertuberkulose, Leipzig u. Wien, 1910.

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What concerns us particularly here is what relation this immunity bears to tuberculin hypersensitiveness. We have already given reasons for our belief that hypersensitiveness to tuberculin is identical with hypersensitiveness to the proteid of the tubercle bacillus and it would seem that the mechanism which gives expression to the tuberculin hypersensitiveness is the same that confers immunity to reinfection. After what has been said it will scarcely be necessary to enlarge upon this view. Its important practical relation is in its bearing on methods of tuberculin treatment. We have it within our power to raise or reduce the sensitiveness of an individual for tuberculin. Which shall we attempt? All things considered, an active reaction to tuberculin is certainly an indication of successful response to the infection and of the development of a high grade of immunity to reinfection. Equally certain is it that the fever and other constitutional symptoms of the disease are hypersensitive or, as contradictory as it may seem, immunity reactions. Experience has shown that with the development of tuberculin immunity by the injection of increasing doses of tuberculin there is a corresponding improvement in these general symptoms. Is the refractoriness here identical with the loss of reacting power frequently observed in individuals with rapidly advancing disease? Too little is known of the mechanism of antianaphylaxis in general to convincingly answer the question but we doubt if they are the same. Perhaps under varying conditions different means will be employed but the matter had best be abandoned here, to be taken up more in detail in speaking of the use of tuberculin in treatment.

Römer¹ has shown that experimentally tuberculin hypersensitiveness runs remarkably parallel with the intensity of the infection, for the more severe the infection

¹ Römer: Tuberkulose u. Tuberkulinreaktion. Beitr. z. Klin. d. Tuberk., 1910, xvii, 427.

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the earlier does the hypersensitiveness appear and the higher is it developed. Using guinea pigs and making weekly intracutaneous tuberculin tests over a long period of time, he obtains material that he charts into most instructive diagrams. The accompanying illustrations, which are selected from a large number, fully demonstrate the relation.

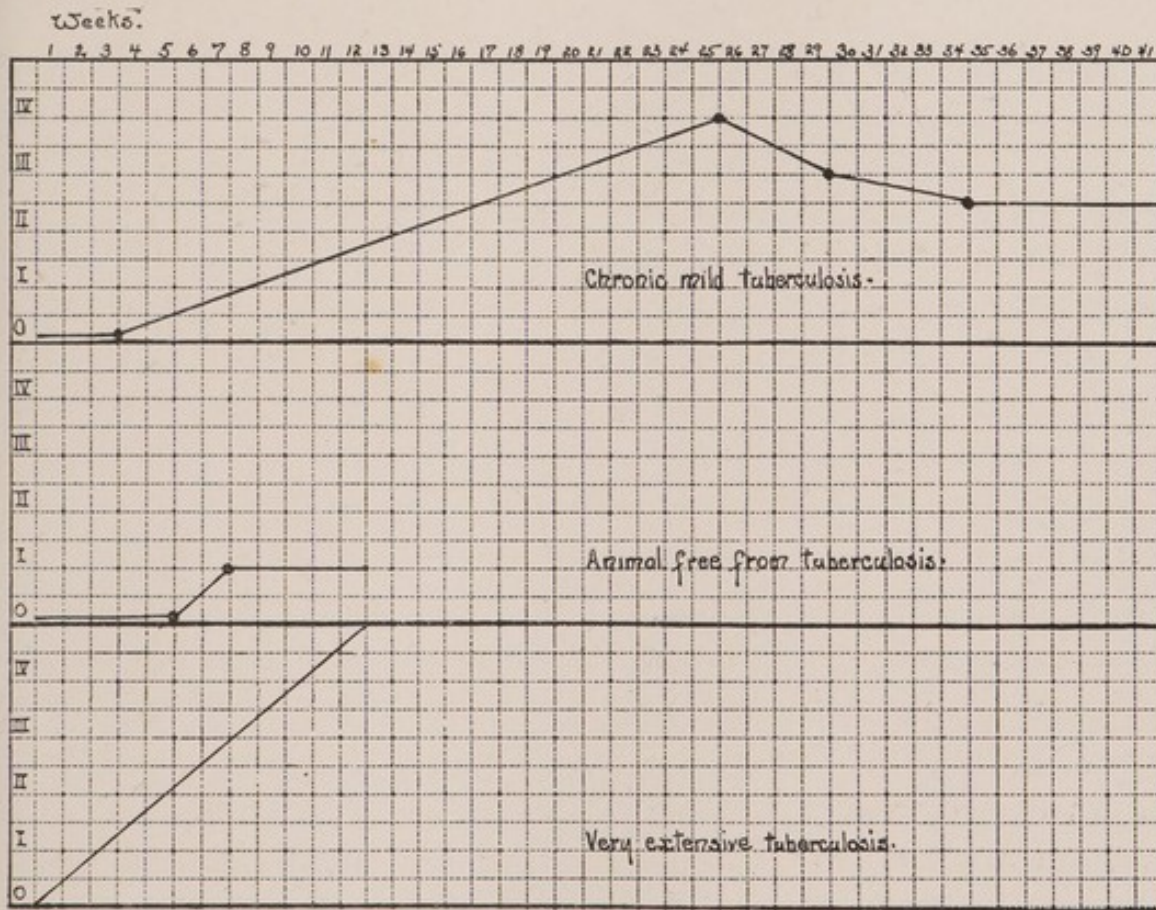


FIG. III.—CHART ILLUSTRATING WEEKLY VARIATIONS IN TUBERCULIN HYPERSENSITIVENESS; AFTER SMALL AND LARGE DOSES OF TUBERCLE BACILLI. (After Römer and Joseph.)

It is possible that in man no such evident correspondence will be found, since the conditions are very different. Spontaneous latent infection in the guinea pig never occurs, while in man it is the predominant form. From the evidence at hand it would seem to be impossible to sharply divide the active from the latent infections on the basis of the degree of tuberculin hypersensitiveness and still less

likely that the latent active and manifest active infections can thus be separated. Quantitative tuberculin tests are, however, just beginning to be made upon man and the results of these investigations must be awaited before reaching a definite conclusion. From our present knowledge it is impossible to give a more detailed account of the mechanism of the immunity conferred by tuberculous infection than to speak of it as a hypersensitive reaction. It is not satisfactorily explained by any of the immunity reactions with which we are at present familiar. Friedberger has sought to associate all anaphylactic phenomena with the precipitin formation, but his work, as we have already stated, awaits confirmation. Römer¹ has applied the methods of demonstrating the various immune antibodies to the serum of his animals of proved strong resistance to reinfection and has found none to correspond regularly with the degree of immunity. Agglutinins are almost constantly present but may not exceed the amount present in normal animals. Immune animals may fail to show complement-absorbing antibodies, while the serum of others completely inhibits hemolysis. They were able to demonstrate no antitoxin in the sense of a substance capable of neutralizing tuberculin. The serum of immune sheep has no influence upon tubercle bacilli allowed to remain a long time in contact with it. It is not possible to passively transfer immunity through the serum from a tuberculous to a non-infected animal.

¹ Römer and Joseph: Beitrag zum Wesen der Tuberkuloseimmunität. Anti-körperstudien. Beitr. z. Klin. d. Tuberk., 1910, xvii, 365.

II

THE USE OF TUBERCULIN IN DIAGNOSIS

THE SUBCUTANEOUS TUBERCULIN TEST

The Choice of Tuberculin.—In the previous section we have said that all products of the tubercle bacillus occasion qualitatively the same reaction. It would be then only consistent to allow that any one of the numerous tuberculin preparations be used for diagnostic purposes. And indeed so they might, but the practice of over two decades has confined itself to a single preparation and this we have continued to use because from past experience we have learned to know its dosage more accurately than that of any other preparation. It would require extensive use to establish the parallel potency of another product and fortunately for the consistent interpretation of results the original tuberculin (O. T.) of Koch has been universally employed. Original tuberculin is prepared by reducing a six-to-eight-weeks-old five-per-cent. glycerin-bouillon culture to one-tenth its volume at 90° C., and filtering. Different products vary somewhat in strength and no accurate method of standardization has been worked out. Their potency may be gaged roughly by determining the fatal dose for tuberculous guinea pigs. The following method, devised by Dönitz, is employed in the official tests made by the German Government.¹ About fifty guinea pigs of approximately equal weight are inoculated subcutaneously with 0.5 mg. of a 12-to-14-day-old bouillon culture of tubercle bacilli. As soon as the animals show symptoms of an active tuberculous in-

¹ Otto: Staatliche Prüfung der Heilsera. Gustav Fischer, 1906.

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fection, which usually happens in three weeks, they are given a preliminary test to decide if they are suitable for the actual potency determination. For this purpose a number of the animals are given 0.3 and 0.5 c. c. standard tuberculin. If the latter dose fails to kill a further length of time is allowed to elapse before giving the test. If fatal it may be undertaken at once. The test is applied by administering to a number of the infected animals descending doses of the standard tuberculin to determine the minimal fatal dose and to a parallel series in the same manner the tuberculin whose strength is to be tested. The death of the animals must occur within twenty-four hours and autopsy show the lesions characteristic of tuberculin intoxication. If the tested tuberculin falls below the standard tuberculin in strength it is discarded; if more toxic, the manufacturers are notified how much to dilute it to make it equal in potency to the standard tuberculin.

This control, carefully carried out, is of the greatest value, for it insures an at least relatively constant action. It is important to use, for diagnostic purposes, only a tuberculin that has been controlled and, unless the standard of comparison employed be the same, not to change from the product of one manufacturer to that of another without being prepared for a difference in results.

The Preparation of Tuberculin Dilutions.—For practical purposes we have found that the simplest method is to prepare a series of dilutions, each serial being one-tenth the volume strength of the former. Bottle No. 1 contains pure tuberculin; No. 2, 9 c. c. diluent and 1 c. c. tuberculin; No. 3, 9 c. c. diluent and 1 c. c. of No. 2; No. 4, 9 c. c. diluent and 1 c. c. of No. 3, etc. The diluent is 0.8 per cent. salt solution with 0.25 per cent. carbolic acid. This plan is simple and very convenient, as the number of the bottle represents the number of figures one must write to express the amount of tuberculin in each c. c. Thus bottle 5 contains

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0.000,1 gm. in each c. c., bottle 7, 0.000,001 gm. per c. c., etc. To administer one milligram we would give one-tenth c. c. of bottle No. 3, 5 mg., 5 c. c. of bottle No. 3, etc. It has been customary to designate the dose of tuberculin in grams and milligrams, while the dilutions are almost invariably made by liquid measurement. This does make a difference in the actual amount administered, but the error is small. The dilutions are best made in wide-mouthed, glass-stoppered bottles. They should be kept in a cool, dark place when not in use. The salt solution must be carefully prepared with distilled water and pure sodium chlorid. Impurities may cause endless annoyance by producing a flocculent precipitate which may not appear until after twelve to twenty-four hours. If the pipettes, bottles and syringes are sterilized there is no danger of contamination. Fresh dilutions should be prepared every two weeks. We have been unable to note any change in strength during this period. To make the dilutions one needs a flask for the sterile salt-carbolic solution, a number of wide-mouthed, preferably glass-stoppered, bottles, and two pipettes, one with relatively large bore, accommodating 10 c. c. of liquid and graduated in tenths, one with finer bore accommodating one-tenth c. c. and graduated in hundredths. The simplest method of procedure is as follows:

To one liter of distilled water add 8 gm. of pure sodium chlorid and 2.5 c. c. of pure carbolic acid. Dissolve, filter into a thin glass flask and plug the mouth with absorbent cotton. The solution is best sterilized in an autoclave, but boiling for fifteen minutes on two consecutive days suffices. If sterilized by boiling, 1,100 c. c. of water should be used to allow for evaporation. It is an advantage to distribute the liter of solution in ten small flasks, each containing 100 c. c., rather than to sterilize it in a large flask. Whenever the tuberculin dilutions are to be prepared a small flask of diluent is used and the remaining portion

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discarded so that the same flask is never used a second time and so danger of contamination avoided. Seven bottles are sterilized by boiling and numbered from two to eight and the date noted upon the label. Into each bottle 9 c. c. of diluent is measured. To bottle 2, 1 c. c. of tuberculin is added and carefully shaken; to bottle 3, 1 c. c. from bottle 2 is added and shaken; to bottle 4, 1 c. c. of bottle 3, etc. If only the high dilutions are required it is economical to begin at bottle three by using 9.9 c. c. diluent and 0.1 c. c. of tuberculin and to prepare the higher dilutions as above, by adding to 9 c. c. diluent 1 c. c. of the contents of the next stronger solution. For diagnostic purposes only dilutions numbers three and four will be required for 0.1 c. c. of number 4 equals 0.1 mg. tuberculin and 1 c. c. of number 3 equals 10 mg., which afford an ample range of dosage.

The injections are made subcutaneously, so that when a local reaction occurs it can be readily detected. An excellent syringe, because with it portions of a cubic centimeter can be satisfactorily measured, is made by the Randall, Faichney Co., and is called the "Tuberculin Sub Q Syringe." The injection may be made into any portion of the body but the region of the back below the angle of the scapula is the desirable situation. Often the arm will be found more convenient and one need not hesitate to make the injection there. Local reactions follow injections into the arm more readily than injections into the back and if the reaction be extensive it is far more painful and incommoding upon the arm. The syringe and needle should of course be boiled before use and care be taken that the tuberculin dilutions remain sterile. The skin needs no other preparation than to be rubbed with alcohol.

The Method of Conducting the Subcutaneous Tuberculin Test.—The clinical conditions in a given case making the administration of the subcutaneous tuberculin test desirable, one begins by carefully observing and recording

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the subjective symptoms of the patient and noting the results of the objective examination. The subjective symptoms that are worthy of special notice vary with the seat of the disease whose tuberculous nature is suspected. For instance, if the patient has pulmonary symptoms the degree of cough, the amount of expectoration and the presence or absence of pain are particularly inquired into. If a vesical lesion is being investigated the frequency of urination and character and degree of pain are most important. In joint lesions one looks to the amount of pain and the mobility.

Long experience has established the temperature as the most trustworthy index of the constitutional reaction and it is indispensable to have an accurate record of its variations. In hospitals it is best to have two hourly rectal measurements for at least two days before the test is given and continued throughout the period of its administration. There need be, however, no hesitancy to apply the subcutaneous tuberculin test to ambulant patients if ordinary care and discrimination be exercised. The patient must keep a record of his own temperature, and a wide experience with dispensary patients has convinced us that even among those of moderate intelligence the records are sufficiently reliable, provided a little patience is used in the instruction. Points to be emphasized are:

1. The thermometer should be held under the tongue with closed lips for at least five minutes before each reading.
2. The temperature should not be taken immediately after the patient has been for some time in the cold.
3. The temperature should not be taken immediately after a hot meal or cold drink.

The average temperature reaction comes on before twelve hours and reaches its maximum between twelve and twenty-four hours. For this reason it is advisable to make the injections either during the early morning hours or late in the evening. If the temperature is not taken dur-

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ing the night, and in ambulant patients it is difficult to have them regularly awakened for this purpose, we deem it best to give the tuberculin between ten in the evening and midnight. The reaction will then rarely begin before the following morning and will usually reach its maximum during the afternoon. There is thus less danger of overlooking a mild reaction, which, though perhaps itself not conclusive, still has an important bearing upon the size of the following dose. Patients should be instructed to take their temperature at any time during the night that they may chance to be awake. It is highly improbable that a reaction of any severity will occur without the patient being awakened. The accompanying figure illustrates a chart that to us has been most satisfactory in recording the temperature and other important features of the tuberculin test. It is planned for pulmonary cases but a few alterations under focal symptoms would make it equally useful in disease of other regions.

It is desirable to have the temperature constantly below 99° before beginning the test and if necessary prolonged rest in bed should be enforced to reduce an existing fever. If, however, after a reasonable period of rest the temperature continues to be daily a little elevated the test need not be indefinitely postponed. It may be satisfactorily administered, provided the patient's condition is otherwise favorable, in spite of a daily rise of not over 100° . We emphasize a daily rise since an occasional rise of temperature might simulate a mild reaction and lead to difficulty in interpretation. These are not ideal conditions for administering the subcutaneous tuberculin test and we must emphasize that it should be given only exceptionally to febrile patients.

The patient should always be carefully examined just before each injection is given and the results carefully compared with what has been previously found and subse-

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| Name: | History No. | | | | Year | | | | Mo. | | | |
|--------------------------|---------------------|--|--|--|------|--|--|--|-----|--|--|--|
| DATE | | | | | | | | | | | | |
| 12 M. | | | | | | | | | | | | |
| 2 A. M. | | | | | | | | | | | | |
| 4 A. M. | | | | | | | | | | | | |
| 6 A. M. | | | | | | | | | | | | |
| 8 A. M. | | | | | | | | | | | | |
| 10 A. M. | | | | | | | | | | | | |
| 12 N. | | | | | | | | | | | | |
| 2 P. M. | | | | | | | | | | | | |
| 4 P. M. | | | | | | | | | | | | |
| 6 P. M. | | | | | | | | | | | | |
| 8 P. M. | | | | | | | | | | | | |
| 10 P. M. | | | | | | | | | | | | |
| TUBERCULIN: | Dose | | | | | | | | | | | |
| | Hour | | | | | | | | | | | |
| PLACE OF INJECTION: | Pain | | | | | | | | | | | |
| | Redness | | | | | | | | | | | |
| | Swelling | | | | | | | | | | | |
| | Enlarged Glands | | | | | | | | | | | |
| FOCAL SYMPTOMS: | | | | | | | | | | | | |
| | Pain in Chest | | | | | | | | | | | |
| | Oppression in Chest | | | | | | | | | | | |
| | Shortness of Breath | | | | | | | | | | | |
| | COUGH: As usual | | | | | | | | | | | |
| | Increased | | | | | | | | | | | |
| | Decreased | | | | | | | | | | | |
| | SPUTUM: As usual | | | | | | | | | | | |
| | Increased | | | | | | | | | | | |
| | Decreased | | | | | | | | | | | |
| | Blood in Sputum | | | | | | | | | | | |
| | Tubercle Bacilli | | | | | | | | | | | |
| CONSTITUTIONAL SYMPTOMS: | | | | | | | | | | | | |
| | Malaise | | | | | | | | | | | |
| | Pain in Limbs | | | | | | | | | | | |
| | Headache | | | | | | | | | | | |
| | Nausea | | | | | | | | | | | |
| | Vomiting | | | | | | | | | | | |
| | Chilliness | | | | | | | | | | | |
| | Restlessness | | | | | | | | | | | |
| | Sleeplessness | | | | | | | | | | | |
| | Eruption | | | | | | | | | | | |
| Flare up of Conjunctiva | | | | | | | | | | | | |
| Flare up of Skin | | | | | | | | | | | | |
| Change in Physical Signs | | | | | | | | | | | | |

DIRECTIONS

While you are receiving tuberculin you must take your temperature every two hours except when you are sleeping. After the first three days note carefully each day in the column opposite the stated symptom whether or not you have it. If you have make a + mark, if you have not make an O. The columns marked "tuberculin," "tubercle bacilli," and "change in physical signs" leave for the doctor to fill in. We are trying to study your case and you must help us by being careful and faithful in keeping your records. If there is anything you do not understand don't guess about it but ask the doctor or nurse

FIG. IV.—HISTORY CHART WITH DIRECTIONS FOR USE.

quently with what is noted during and after the reaction. This is by far the most important detail in administering

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the test and the one most difficult to control, since the comparisons must rest largely upon personal impressions. If the disease is external, such as cutaneous, ocular and laryngeal lesions, its appearance should be minutely studied; if inaccessible to sight, its manifestations should be observed by every applicable method of examination.

The preparatory observations having been made the initial dose to be selected and the following amounts will somewhat depend upon the main object one has in view in administering the test. The object may be:

1. To establish that the patient is hypersensitive to tuberculin.

2. To elicit a focal reaction.

It is true that the second includes the first, but the manner of procedure will be influenced by the aim one has in mind. As a rule focal reactions are more easily appreciable when the general reaction is well marked, while hypersensitiveness may be demonstrated by employing much smaller doses and the patient thus be spared the discomfort of severe constitutional symptoms. We shall point out later why we feel that the subcutaneous test need no longer be resorted to, at least not as a routine measure, to establish a patient's hypersensitiveness for tuberculin. This may now be done quite as satisfactorily by far simpler and much less disturbing methods. Before the introduction of the cutaneous and conjunctival tuberculin tests we employed the subcutaneous test regularly to gage hypersensitiveness, while now we use it almost exclusively to attempt the detection of focal reactions, and we are firmly convinced that this will ultimately come to be its place in tuberculin diagnosis.

Koch's original directions for diagnosis were to give one milligram, then five, then ten and if no reaction follows this dose to repeat it. This plan was rigidly followed for many years before any notable deviations were introduced.

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It was frequently noted that severe reactions follow the initial dose of one milligram and there has been a general tendency to make the first dose smaller. As a routine this change is desirable, although it need not be constantly followed. Hutinel¹ in France and Pickert in Germany² were the first to suggest remaining at small doses instead of

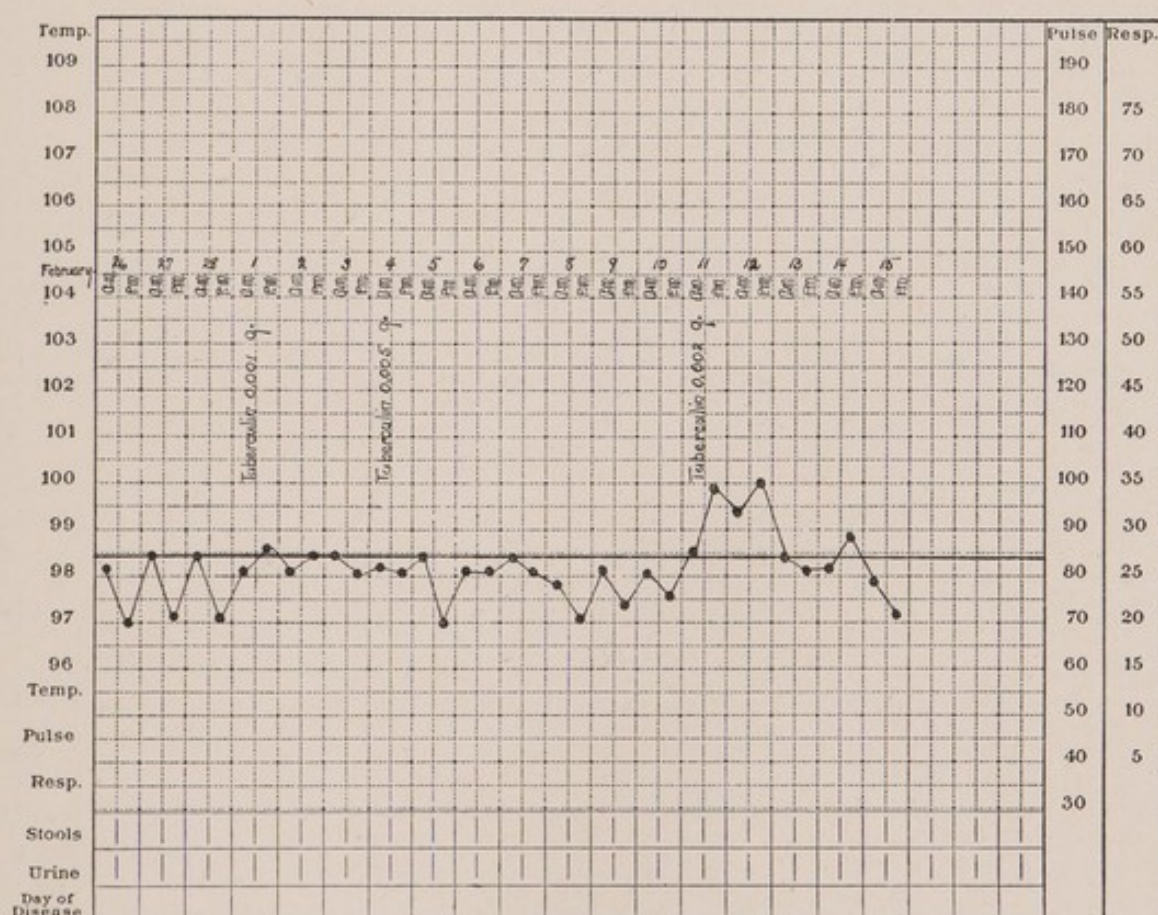


FIG. V.—CHART ILLUSTRATING THE INCREASED SENSITIVENESS OCCASIONED BY A SMALL DOSE OF TUBERCULIN. There is no reaction to 1 mg. nor to $\frac{1}{2}$ mg. but a decided reaction to the third injection of $\frac{1}{4}$ mg.

ascending to the usual high amounts. The plan was further elaborated by Löwenstein and Rappaport³ who, in

¹ Hutinel, cited Jordan and Fischer: *Le diagnostic précoce de la tuberculose pulmonaire*. Paris, 1901.

² Pickert: *Zur Tuberkulindiagnose in der Heilstätte*. *Ztschr. f. Tuberk.*, 1903, iv, 21.

³ Löwenstein and Rappaport: *Über den Mechanismus der Tuberkulinimmunität*. *Ztschr. f. Tuberk.*, 1904, v, 485.

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1904, published the results of their interesting studies on hypersensitiveness to tuberculin, showing that decided reactions may be produced by the repetition of small doses. They claim that in the majority of cases a four-time repetition of one-fifth of a milligram will liberate a reaction in the tuberculous and that only occasionally is it necessary



FIG. VI.—CHART ILLUSTRATING THE INCREASED SENSITIVENESS OCCASIONED BY A SMALL DOSE OF TUBERCULIN. A mild reaction follows 1 mg., a much more severe reaction the second injection of $\frac{1}{2}$ mg.

to ascend to higher doses. The accompanying charts show such a reaction. Roepke,¹ Hamman² and others, however, have demonstrated that so many definitely tuberculous cases fail to react to this method that it is of little value

¹ Roepke: Über diagnostische Tuberkulindosen. Ztschr. f. Tuberk., 1907, x, 412.

² Hamman: The use and the value of tuberculin in the diagnosis of pulmonary tuberculosis. Arch. Int. Med., June, 1908.

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in practice. Still the results of Löwenstein and Rappaport cannot be too greatly emphasized, for they are the first to have made clear how a dormant hypersensitiveness may be aroused by tuberculin injections and to have discarded the older view of a summation of doses. A further conclusion from their results is that a reaction to a second or third

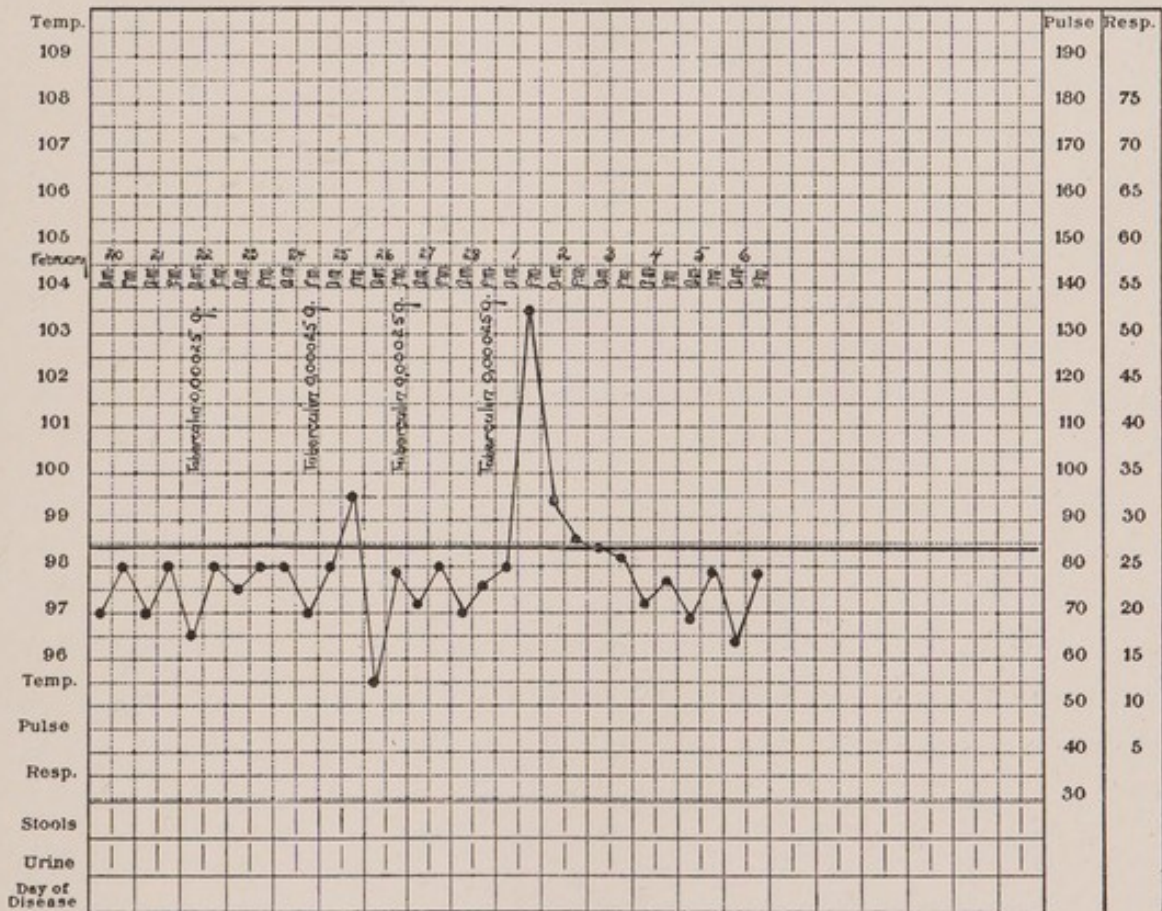


FIG. VII.—CHART ILLUSTRATING A SLIGHT REACTION TO THE SECOND DOSE OF $\frac{1}{8}$ MG. OF TUBERCULIN AND A SEVERE REACTION TO THE FOURTH INJECTION OF THE SAME DOSE.

injection of tuberculin has not the same significance as a reaction to an initial dose. We have given the evidence upon which we base the assertion that tuberculin, as ordinarily administered, never gives rise to hypersensitiveness, although it may exaggerate a mild grade of hypersensitiveness associated with a dormant tuberculous focus. A reaction to a primary injection signifies, therefore, a

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higher degree of hypersensitiveness than does a reaction to the same amount administered after one or more preceding doses. The importance of this principle is demonstrated by the reaction one occasionally produces with descending doses.

If the object in administering tuberculin is to establish the presence or absence of tuberculin hypersensitiveness, mild reactions will suffice and for the purpose small doses repeated or gradually increasing amounts may be given. If one aims to produce an appreciable focal reaction larger doses and a more rapid increase are desirable. Roepke has suggested one-fifth mg., one milligram, five milligrams as the best plan and after trying many variations we have come ourselves to adopt these doses as the most generally satisfactory. We hasten to add that they are not to be employed indiscriminately as a routine, for it is of the greatest importance that our method be changed to meet varying indications. We will suppose that the patient, after the required preliminary observation, has received the fifth of a milligram as the initial dose. On the following day the temperature is carefully watched, the point of injection inspected and the diseased area examined. If at the end of forty-eight hours there has been no evidence of a reaction the second dose is administered, and if no reaction follows this forty-eight hours later the third. The interval between doses should never be less than forty-eight hours and it is advisable not to have it exceed seventy-two hours. Although it is unusual for a reaction to occur after twenty-four hours have passed uneventfully, exceptionally it may be delayed until thirty-six hours after an injection and it would be very undesirable to add a second dose of tuberculin during the preliminary period of a reaction. Very severe symptoms might thus be engendered needlessly. On the other hand, the hypersensitiveness stimulated by an injection of tuberculin reaches its maximum intensity in

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from ten to fourteen days and it is a disadvantage to delay the completion of the test longer than is necessary.

If following an injection of tuberculin there is any evidence of a reaction, however slight it may be, the amount must not be increased but the same dose repeated. In many instances such a repetition will be followed by a definite reaction but if no reaction occurs a larger dose may then be given. As evidence of such mild premonitory reactions we may note alterations in the temperature, in the general constitutional condition or at the site of the injection. We practically never obtain convincing evidence of a focal reaction without accompanying general symptoms. The temperature is the most delicate index and a rise of half a degree or more should at once awaken a suspicion which becomes an assurance if a local reaction is also discovered. The same dose repeated will then almost constantly produce a decided reaction. A local reaction, redness and infiltration at the site of injection, without temperature elevation, is not so important an indication. It is the rule that injections preceding the one liberating a general reaction produce local reactions and indeed each succeeding dose may be followed by extensive infiltration at the site of injection, although no febrile or constitutional reaction be produced. Still when a well-marked local reaction occurs it is advisable to proceed cautiously if we desire to avoid a severe general reaction. Patients will occasionally complain that they feel depressed and indisposed following the injection of tuberculin although there is no other indication of a reaction. It is, however, very rare to obtain definite constitutional symptoms in the absence of temperature elevation.

The best terminal dose in subcutaneous tuberculin diagnosis has been keenly discussed. Bandelier,¹ in a lengthy

¹ Bandelier: Die Tuberkulindiagnostik in den Lungenheilstätten. Beitr. z. Klin. d. Tuberk., 1904, ii, 285.

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article, has insisted that Koch's original limit of ten milligrams be rigidly adhered to and that perfectly satisfactory results can be obtained only by repeating this dose when its first administration is not followed by a reaction. Roepke¹ in a large number of cases found that proportionally as great a number of reactions occurred, using five milligrams as the terminal dose, as by using ten milligrams, and concluded that for practical purposes one need not go beyond five milligrams. In their more recent publication² these authors have reached a compromise, Bandelier omitting the repetition of ten milligrams and Roepke admitting the advisability of giving ten milligrams once. The plan they now advocate is to give one-fifth milligram, then one, then five, and finally ten milligrams. Bandelier's argument on the necessity of repeating ten milligrams rested upon the observation that among five hundred patients thirty-six who had failed to react to ten milligrams did react when the dose was repeated, and a few of these even showed a focal reaction. We shall leave until later the discussion of these focal reactions and consider only the general reaction to the second ten milligrams. Of the 500 patients only thirty-seven remained who showed no reaction following this repetition and Bandelier, in a fine spirit of curiosity, pushed the investigation further. Twelve of these negative cases were given still larger doses of tuberculin and four reacted to twenty milligrams and six to forty. From these results Bandelier draws the naïve conclusion that even healthy individuals will react to twenty milligrams of tuberculin although the only clinical means of differentiating these healthy individuals from the tuberculous is the fact that they have failed to react to ten milli-

¹ Roepke: Die Ergebnisse gleichzeitig angestellter kutaner, konjunktivaler und subkutaner Tuberkulinreaktionen. Beitr. z. Klin. d. Tuberk., 1908, ix, 353.

² Bandelier and Roepke: Lehrbuch der spezifischen Diagnostik und Therapie der Tuberkulose. 4th edition. Würzburg, 1910.

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grams given a second time. For Bandelier tells us that as far as symptoms and physical signs go they were indistinguishable from those that did react, and he looks upon this differentiation with tuberculin as the only means of placing sanatorium results upon an irreproachable basis.

We ourselves view the discussion of the optimal terminal dose as without practical significance. We have pointed out at length why it is impossible to hit upon a dose that will separate clinically healthy from clinically tuberculous individuals, or one that will invariably distinguish latent from active infections. Unfortunately, the degree of tuberculin hypersensitiveness does not vary in direct proportion to the activity of the disease but depends upon so many unknown factors that we are unable to accurately formulate its conditions. A certain number of individuals who fail to react to five milligrams will react to ten, some who do not react to ten will react to fifty and so on. Goetsch has insisted that one must give fifty milligrams of tuberculin to definitely exclude tuberculosis, but even this amount is quite arbitrarily chosen. The optimal terminal dose will then be largely determined by what we wish it to indicate. We seek to administer a dose large enough to exclude active clinical tuberculosis. While hypersensitiveness to tuberculin is often as well marked in individuals with latent active lesions as in those with manifest active lesions and a positive tuberculin reaction does not accurately distinguish the two when a reaction fails to occur after a sufficiently large dose, it does with reasonable probability exclude existing active and recently acquired lesions. Quantities larger than this do with still greater probability exclude active lesions but include among those who react more and more latent cases so that what is gained on the negative is more than lost on the positive side. We shall return to this important question in considering the value of tuberculin in diagnosis and refer to it

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here only to point out its applicability to the question of the optimal terminal dose. In our experience a terminal dose of five milligrams accomplishes all that we have a right to ask of the subcutaneous tuberculin test, for it reasonably excludes active tuberculous lesions. Only occasionally do we give larger amounts. For instance, if an individual has marked symptoms and physical signs of a tuberculous lesion and still fails to react to five milligrams, it is an added assurance against the tuberculous nature of the disease if he also fails to react to ten milligrams.

As a routine, then, we have adopted the plan to give one-fifth milligram of tuberculin as the initial, one milligram as the second and five milligrams as the end dose. We have said that the plan is only a general guide and must be varied to meet special conditions. The most important of these, the repetition of the dose, or at least only a slight increase when it is followed by the development of symptoms suggesting a mild reaction, we have sufficiently emphasized. We have also spoken of the occasional advisability of going to larger amounts than five milligrams to confirm a negative result that is at variance with the clinical impression. Besides these, the condition of the patient is important. In anemic and poorly nourished individuals and in the highly neurotic smaller doses and a more gradual ascent may be advisable.

The foregoing description of doses for tuberculin diagnosis is given for adults; in children smaller amounts must be used. The constitution of the child and what we wish to accomplish will largely guide us. In children from eight to fourteen years of age an initial dose of one-tenth milligram and a terminal dose of one milligram, with one or two intervening doses, may be adopted as a general rule. In delicate children the amounts should be smaller and the ascent more gradual.

The Clinical Symptoms of Hypersensitiveness Mani-

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tested to **Subcutaneous Injections of Tuberculin**.—The characteristic features of a tuberculin reaction are:

1. Constitutional symptoms.
2. A local reaction.
3. A focal reaction.

The constitutional symptoms as a rule appear in from six to twelve hours after the injection, reach their height in from six to twelve hours later and then subside so that the whole reaction is over in from twenty-four to thirty-six hours. These intervals are only very relative outlines, for they vary endlessly. The reaction may begin after four hours or it may be delayed to thirty-six; it may begin abruptly with a chill or come on more gradually; the subsidence of the temperature and symptoms may occur as rapidly as the rise.

The most important of the constitutional symptoms is the fever. It can be observed and accurately studied more readily than the others and for this reason has come to occupy a commanding position. Although the other constitutional symptoms are not always proportionate to its extent, the character and severity of the reaction are gaged by it. In general, reactions during which the temperature does not exceed 100° are spoken of as mild; the high point between 100° and 102° as moderate; over 102° as severe reactions. The question to what height the temperature must rise in order to consider a reaction positive has no longer the importance it formerly had when the febrile reaction was given almost exclusive consideration. We now look to related phenomena to assist in reaching a conclusion. The question, however, has been given so much prominence that it may be well to say a few words about it. It is not uncommon, for instance, during the administration of the tuberculin test, to observe a slight temperature elevation after an injection unaccompanied by any decided subjective symptoms. Usually a repetition of the same amount

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will then liberate a decided reaction but often not only is there no reaction to the repeated dose but higher amounts fail to elicit one. The failure to react to larger doses is held to abolish the suspicion surrounding the original temperature elevation and to stamp it as not due to tuberculin. Such unexplainable temperature elevations give more concern and annoyance during tuberculin treatment than during diagnosis, but even in diagnosis are perplexing. They are particularly important since numerous investigators have observed febrile elevations, in no way distinguishable from the temperature rise of a tuberculin reaction, follow injections of salt solution or merely the insertion of a hypodermic needle. Before the specificity of the local reaction was fully appreciated such fevers, usually ascribed to a neurosis, were extremely confusing. We have come ourselves to rely entirely upon the presence or absence of a reaction at the site of injection as a guide to the interpretation of such questionable reactions. Our experience is not large enough to permit us to say that a febrile reaction to tuberculin never occurs in the absence of a local reaction but such an occurrence must be rare, for as far as our experience goes we have never observed a definite tuberculin reaction without the presence of a local reaction to the same or to preceding doses. It is common enough to observe intense local reactions in the absence of temperature elevation and as the dose is raised to obtain suddenly a severe febrile reaction but to this dose no, or only a slight, local reaction.

A more difficult question to answer is whether the subcutaneous tuberculin test may be considered positive without an elevation of temperature. We come here, not upon fundamental differences, but upon differences of definition. Unquestionably a patient who gives a distinct local reaction to an injection of tuberculin displays tuberculin hypersensitiveness and reacts to tuberculin even if there is no

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elevation of temperature. Still, as fever has come to be generally regarded as the essential criterion of the subcutaneous test, it seems best to continue to call such instances negative to the subcutaneous tuberculin test in spite of the local reaction. Just how high the temperature must go to constitute a positive subcutaneous test is not uniformly

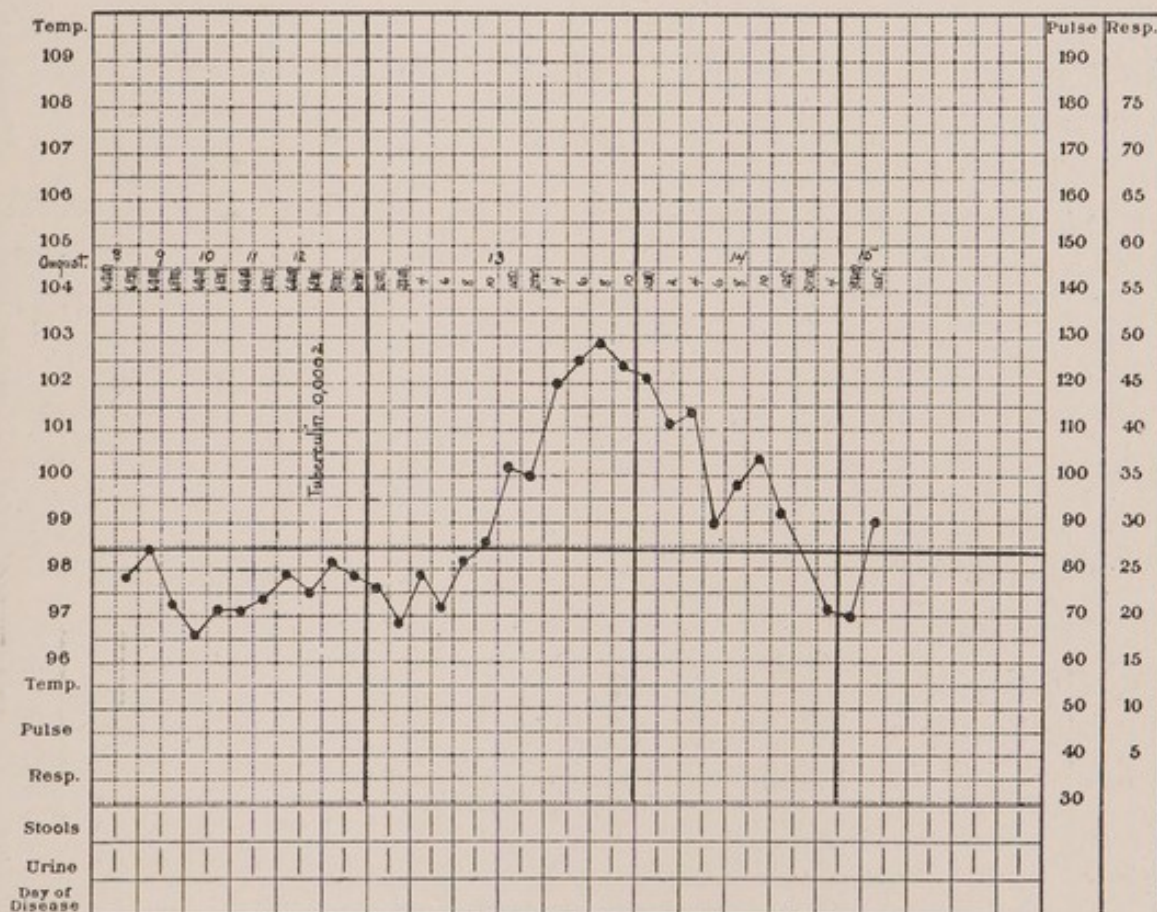


FIG. VIII.—CHART ILLUSTRATING A CHARACTERISTIC TUBERCULIN REACTION.

agreed upon. We regard an elevation of one degree Fahrenheit above the previous maximum temperature as sufficient.

The fever accompanying tuberculin reactions generally rises abruptly, reaching the fastigium in from six to eight hours, and then falls more gradually to normal or to subnormal. There are, however, endless variations from this type. It may rise with great abruptness and fall equally rapidly, the whole reaction being over in from four to six

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hours. Frequently the fall is broken by a secondary rise which may come on after the temperature has reached normal. These differences may be seen in the accompanying charts and as they have no special clinical significance we shall not analyze them in detail. It may be said that as a general rule prompt reactions indicate a fresh invasion,

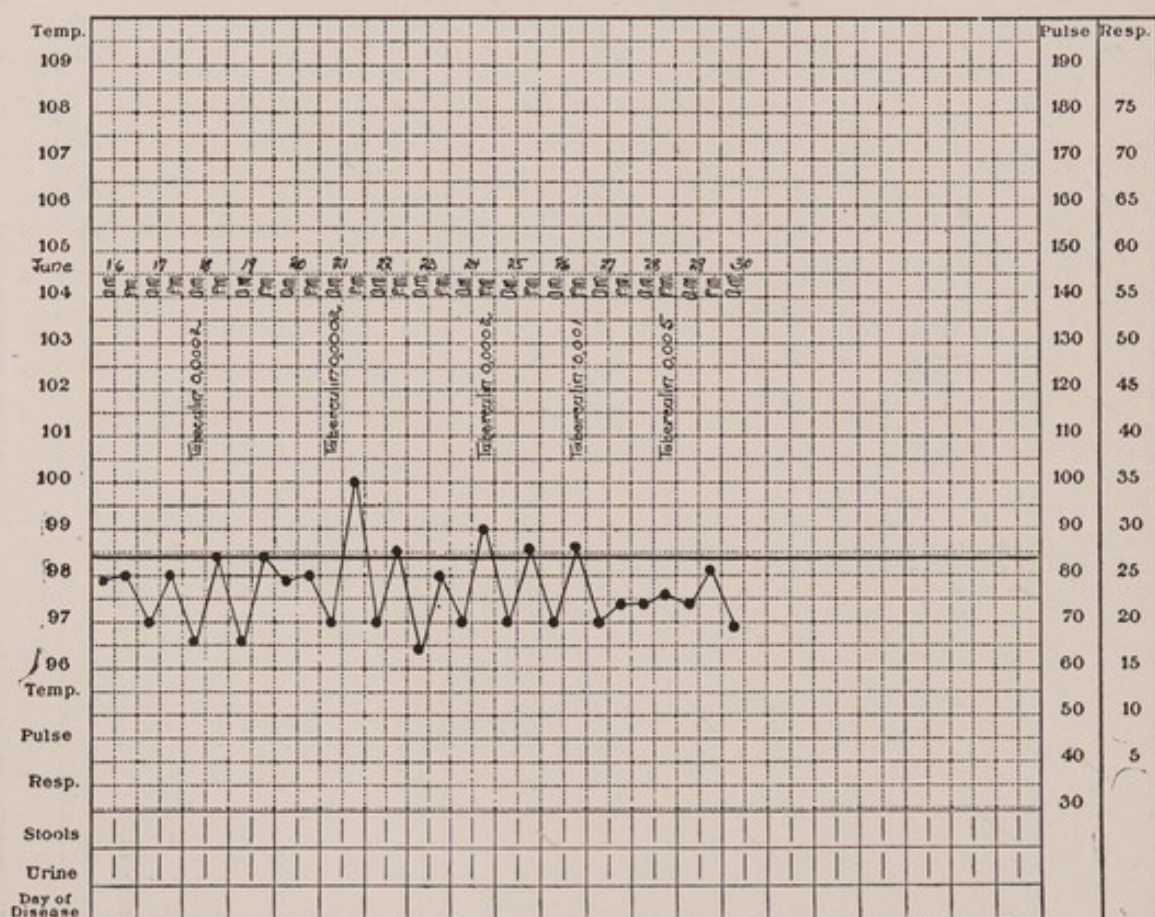


FIG. IX.—CHART ILLUSTRATING A PSEUDO-TUBERCULIN REACTION. The temperature rises to 100° after a second dose of $\frac{1}{2}$ mg., but there is no further reaction even to 5 mg.

while delayed reactions point to chronic or inactive lesions.

The constitutional symptoms associated with the temperature elevation are varied. During typical reactions they are very like the symptoms of an influenza infection. The patient feels depressed and achey, has severe pains in the joints and back, intense headache and great loss of muscular power. Nausea and vomiting are frequently pres-

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ent. The symptoms usually quickly subside, although if the reaction has been very severe prostration may persist for a day or two. Hammer¹ has given a detailed analysis of the frequency of the different symptoms. During the height of the reaction delirium may occur. In epileptics a convulsion may be inaugurated. An eruption of herpes is

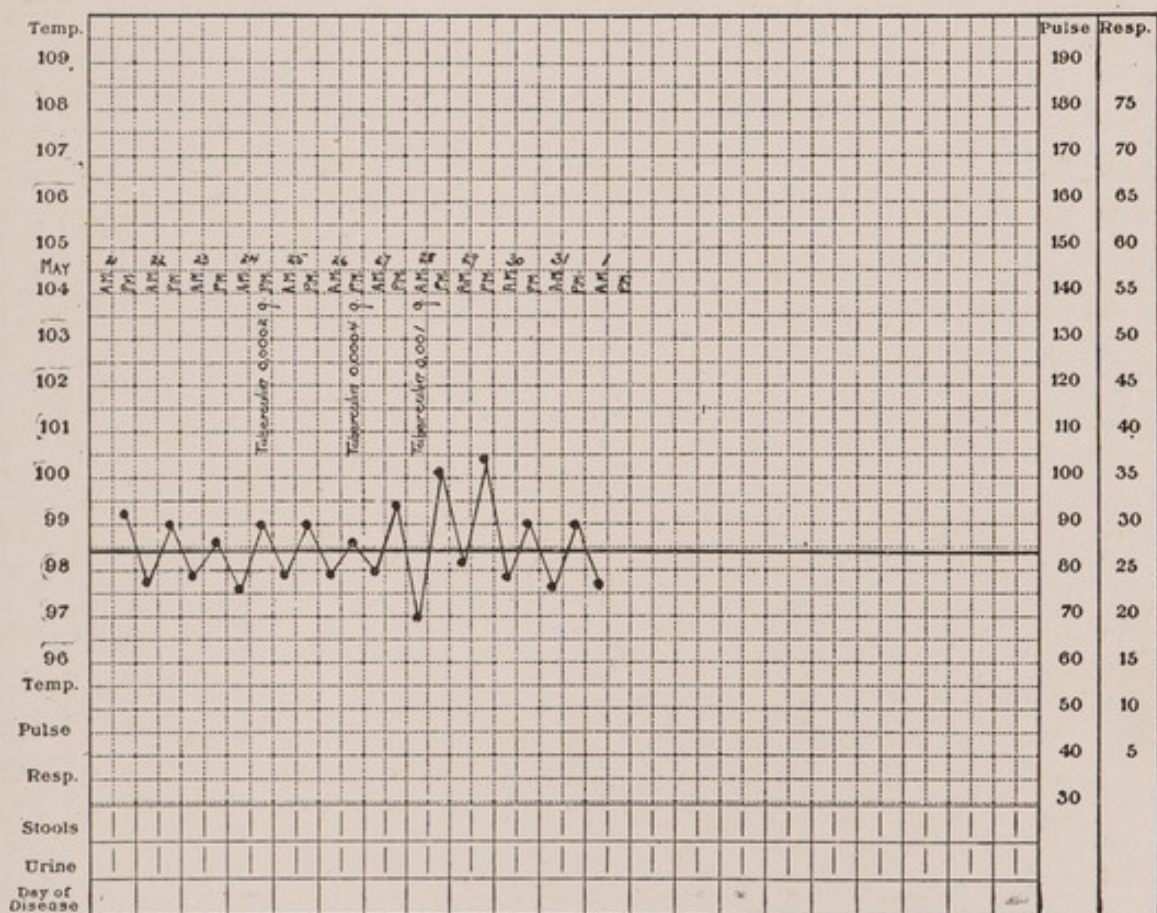


FIG. X.—CHART ILLUSTRATING A CHARACTERISTIC TUBERCULIN REACTION WITH A SECONDARY RISE OF TEMPERATURE.

not uncommon. The intensity of the symptoms does not always run parallel with the height of the temperature. Occasionally patients with a febrile reaction to 104° will complain of little general disturbance, while an elevation of one degree may be associated with intense prostration.

¹ Hammer: Über die diagnostische Tuberkulininjektion und ihre Verwendung beim Heilstättenmaterial. Beitr. z. Klin. d. Tuberk., 1903, i, 325.

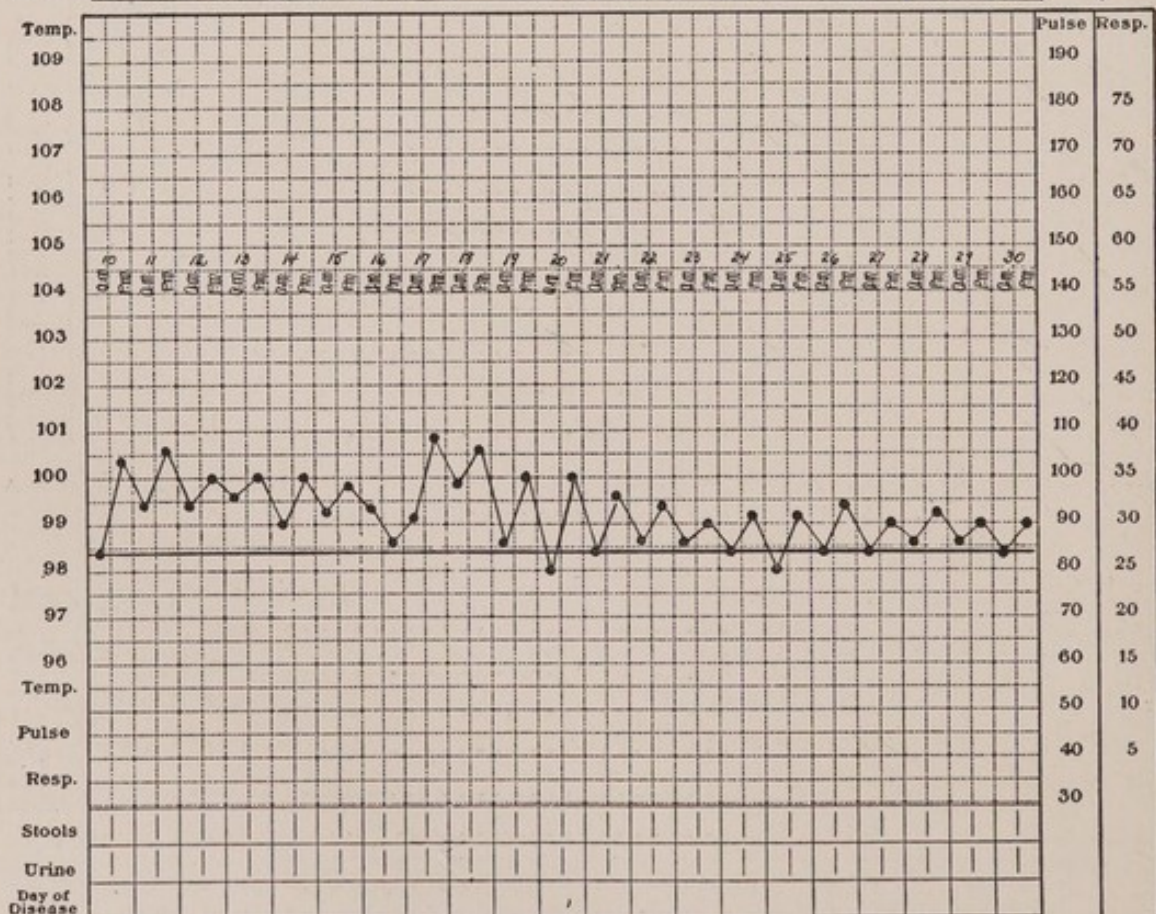
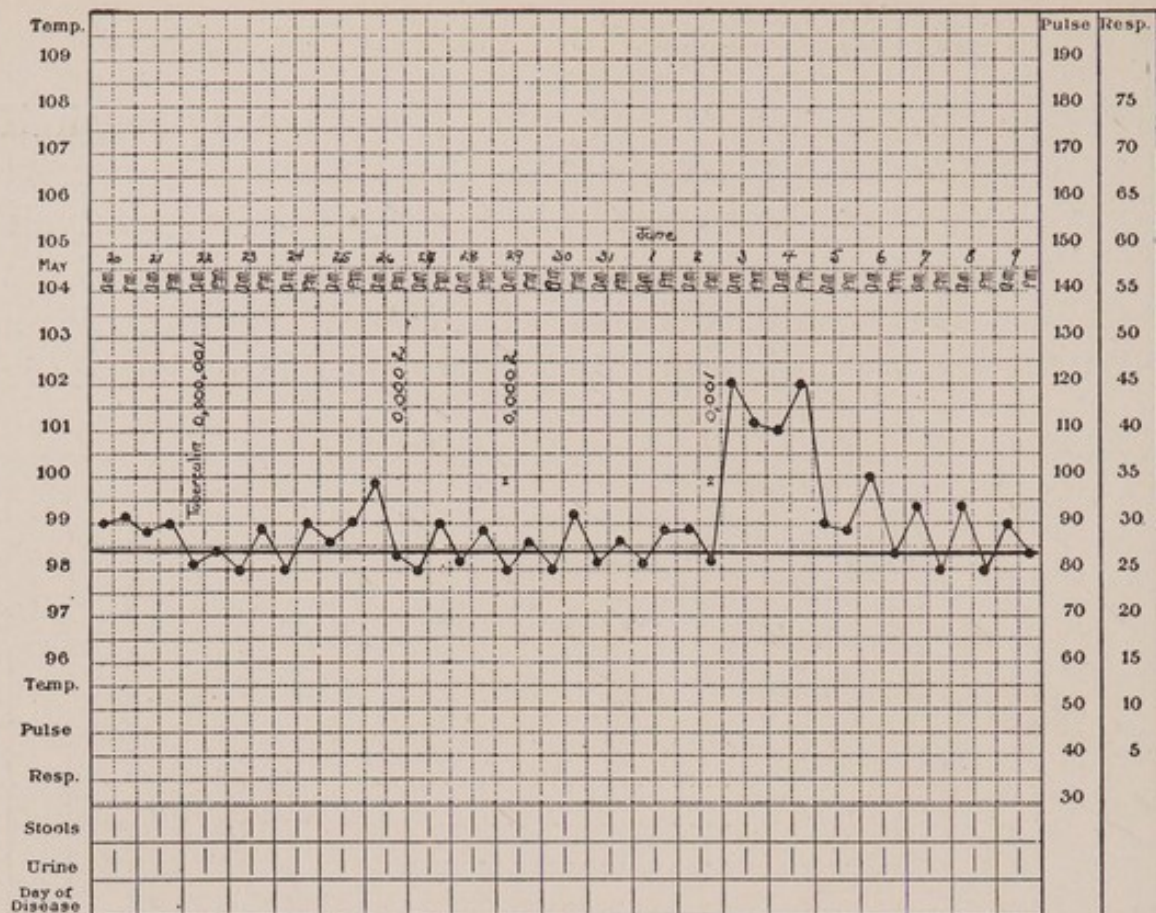


FIG. XI.—CHARTS SHOWING A PROLONGED PERIOD OF PYREXIA AFTER A TUBERCULIN REACTION.

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Indeed patients frequently complain of general malaise and indisposition even in the absence of fever.

The local reaction consists of redness and swelling at the site of the injection. Histologically the infiltration presents the structure characteristic of tuberculous tissue. In extent it varies from slight redness to areas of subcutaneous swelling as large as a hen's egg. The regional glands are frequently swollen and tender, the swelling being due to an acute inflammatory hyperplasia. The local reaction is absolutely specific, indicating the presence of tuberculin hypersensitiveness. It is usually more marked after the injection preceding than after the one liberating a general reaction. We have already discussed its relation to the general reaction.

The focal reaction consists in an inflammatory reaction about the focus of disease. As a practical rule we may accept that such a focal reaction always occurs when there is a general constitutional reaction although its absolute necessity for constitutional symptoms to appear is open to discussion.¹ When the tuberculous lesion is situated externally its occurrence may be easily observed and we do not feel that we can improve upon Koch's original description of the changes that occur.² When the suspected lesion is situated internally the symptoms and signs that the focal changes induce will vary with the seat of the lesion. These we shall consider in speaking of the use of tuberculin in the diagnosis of tuberculosis of various organs. Unfortunately, they are frequently not definite enough to be convincing and in their absence the conclusion that a focal reaction has not occurred is never justified.

The Results of the Application of the Subcutaneous Tuberculin Test.—The most extensive figures we have of the results of the application of the subcutaneous tubercu-

¹ See page 26.

² See page 4.

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lin test to a varied clinical material are those gathered by Beck¹ from the records of the Institute for Infectious Diseases in Berlin. From the summer of 1891 to the fall of 1897 there were 4,254 admissions to the hospital and of these 2,505 submitted to the test. The method used was to give 1, then 5, then 10 mg. The following table is constructed from Beck's report:

| Disease | No. of Cases | Reacted |
|---------------------------------------|--------------|---------|
| Tuberculosis | 378 | 378 |
| Suspected pulmonary tuberculosis..... | 338 | 298 |
| Influenza | 106 | 67 |
| Pleurisy | 68 | 50 |
| Bronchitis | 66 | 29 |
| Croupous pneumonia | 76 | 27 |
| Emphysema | 14 | 4 |
| Empyema..... | 1 | 0 |
| Glands in neck..... | 17 | 16 |
| Scrofula | 2 | 2 |
| Adenoids | 13 | 12 |
| Ozena | 4 | 3 |
| Erysipelas | 121 | 59 |
| Addison's disease | 1 | 1 |
| Puerperal sepsis | 5 | 2 |
| Phlegmon | 4 | 2 |
| Abscess | 4 | 2 |
| Tonsillar abscess | 6 | 3 |
| Anemia | 36 | 19 |
| Diabetes mellitus | 5 | 1 |
| Typhoid | 58 | 27 |
| Muscular rheumatism | 31 | 23 |
| Articular rheumatism | 82 | 46 |
| Diphtheria | 50 | 11 |
| Tonsillitis | 127 | 47 |
| Scarlatina | 49 | 18 |
| Measles | 26 | 8 |
| Small-pox | 6 | 1 |
| Exanthems | 11 | 3 |
| Eczema | 15 | 7 |
| Favus | 1 | 1 |

¹ Beck: Ueber die diagnostische Bedeutung des Koch'schen Tuberkulins. Deutsch. med. Wehnschr., 1899, xxv, 137.

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| Disease | No. of Cases | Reacted |
|-----------------------------------|--------------|---------|
| Psoriasis | 3 | 2 |
| Basedow's disease | 1 | 1 |
| Gonorrhea | 106 | 59 |
| Soft chancre | 57 | 26 |
| Syphilis | 143 | 59 |
| Gastritis | 47 | 25 |
| Gastric ulcer | 15 | 10 |
| Gastroenteritis (adults) | 62 | 29 |
| Perityphlitis | 13 | 7 |
| Cystitis | 8 | 5 |
| Nephritis | 17 | 4 |
| Heart disease | 16 | 10 |
| Jaundice | 4 | 1 |
| Tapeworm | 1 | 1 |
| Pelvic inflammatory disease | 107 | 51 |
| Fluor | 21 | 11 |
| Abortion | 55 | 11 |
| Puerperium | 5 | 5 |
| Mastitis | 2 | 2 |
| Sarcoma | 5 | 2 |
| Carcinoma | 20 | 4 |
| Poisoning | 3 | 1 |
| Neurasthenia | 23 | 12 |
| Tabes | 5 | 1 |
| Hysteria | 13 | 3 |
| Epilepsy | 2 | 1 |
| Herpes zoster | 1 | 0 |
| Erythema nodosum | 1 | 0 |
| Leprosy | 3 | 3 |
| Laryngeal ulcers | 25 | 17 |

We may say that our totals are a little different from those given by Beck, for we have been unable to add up the individual items to correspond with his sums. Where the difficulty lies we have been unable to determine and have given our additions. The difference between the two is so small that the conclusions are not practically altered. Certain errors, probably oversights, exist in the figures he gives. For instance, he says of 31 cases of muscular rheumatism 23 reacted and 18 did not. It will be seen that we have accepted the positive numbers. In referring to the

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infectious diseases it will of course be understood that the test was given during convalescence.

Of 2,505 patients receiving the subcutaneous test 1,530, or 61 per cent., reacted. Of this number 396 were definitely tuberculous and all reacted. This includes 371 cases of outspoken pulmonary tuberculosis, two cases of intestinal tuberculosis, five cases of urogenital tuberculosis, two cases of scrofula and sixteen cases of tuberculous cervical adenitis. There were 17 cases of adenitis thought to be tuberculous but one of these failed to react to tuberculin and histological examination demonstrated the glands to be sarcomatous. Of 338 cases of suspected pulmonary and 25 cases of suspected laryngeal tuberculosis, 315 cases, or 86.8 per cent., reacted. Subtracting these definitely and probably tuberculous cases from the total number there remain 1,746 patients with no clinical evidence of tuberculous disease, of which number 819, or 47.9 per cent., reacted. It may be justly urged that pulmonary tuberculosis frequently lurks behind the mask of pleurisy, influenza, bronchitis and emphysema and that we run a grave risk of error in admitting these as non-tuberculous affections. This is notably true of pleurisy. By further subtracting these four groups of cases 1,492 remain, of which number 669, or 44.16 per cent., reacted.

Next in importance to the figures of Beck are those collected by Franz,¹ who tested 400 recruits in the Austro-Hungarian army by injecting 1, then 2, then 3 mg. of tuberculin. In a few instances 5 mg. was given as the terminal dose. The soldiers were in a regiment recruited from Bosnia, where tuberculosis is prevalent. Two hundred and forty-five, or 61 per cent., reacted. To determine the constancy of the reaction he reinjected 100 of the men at the

¹ Franz: Ergebnis mehrjähriger Beobachtungen an tausend im Jahre 1901 und 1902 mit Tuberkulin zum diagnostischen Zwecke, injizierten Soldaten. Wien. klin. Wehnschr., 1909, xxii, 991.

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end of a year. All those who had previously reacted reacted again to the same or to smaller doses. Fourteen instances previously negative now reacted, making 76 per cent. positive against the initial 61 per cent.

This increase in the percentage of reactions may be explained by supposing that infection had occurred during the year in the fourteen cases or that the previous injections had stimulated a dormant hypersensitiveness. Franz mentions both possibilities, but while he emphasizes the first we should by all means lay chief stress upon the second. Of 321 soldiers from the same regiment tested the following year 222, or 68.8 per cent., reacted. In order to control these surprising results Franz drew 279 soldiers from a Hungarian regiment recruited in a province notably free from tuberculosis. Whereas in the Bosnian regiment roughly 60 per cent. of the incapacity was caused by outspoken or probable tuberculous disease, in this particular Hungarian regiment it had caused, during the same period, but 24.8 per cent. One hundred and eight, or 38.7 per cent., of the men reacted. It should be emphasized that all of the soldiers were healthy, vigorous, young men between the ages of 21 and 23 years.

After three years of service among 1,002 men tested with tuberculin 46 developed tuberculous disease, and in from three to four years after discharge from the army 18 more had developed the disease. In the Hungarian regiment 3.2 per cent. became tuberculous, in the Bosnian 7.6 per cent. Of the 64 men who developed tuberculosis within seven years after the test, the reaction had originally been positive in 46, negative in 18; of these 18, 12 developed tuberculosis within three years after the test. All but 3 of the 18 cases had slowly progressing chronic lesions and Franz believes that they must have been infected at the time they failed to react. Therefore he concludes that three milligrams of tuberculin is not a large enough dose

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to reveal all infections, but adds that had he gone to ten milligrams he is convinced that his figures would parallel the anatomical figures of Naegeli. He could find no relation between the severity and the duration of the reaction and the time of onset and course of the subsequent tuberculous disease. Nor did the development of the disease bear any relation to the size of the dose that elicited a reaction. There was no difference in the type of reaction in those who did and those who did not develop tuberculosis.

These two sets of figures are by far the most important that we possess of the tuberculin test, not merely in point of number but also on account of the character of the material. Other large statistics have been gathered by the application of the test to individuals clinically suspected of having tuberculosis and are therefore not nearly so valuable in many directions. A few of the most important of these we will quote. Fraenkel¹ reports 200 observations. Fifty-six cases of pulmonary tuberculosis all reacted; 76 cases suspected of having pulmonary tuberculosis, 70, or 92.1 per cent., reacted; 68 cases without any suspicion of tuberculosis, 37, or 56.1 per cent., reacted. Hammer gave the test to 180 ambulant patients; 139 were either definitely tuberculous or very probably so, 132 reacted. Of 41 doubtful cases 32 reacted. Ten mg. was the usual terminal dose.² Bandelier³ gave 500 sanatorium patients the test. All had symptoms or physical signs that pointed toward the presence of a tuberculous pulmonary lesion but none had tubercle bacilli in the sputum and in none were the signs perfectly conclusive. One hundred and seventy-three of the 500 reacted to the initial dose of 1 mg.; 156 to 5 mg.; 98 to 10 mg. and 36 to the second dose of 10 mg.; 37, or 7.4

¹ Fraenkel: *Lungenkrankheiten*. Berlin, 1904, 842.

² Hammer: *Ueber die diagnostische Tuberkulininjektion u. ihre Verwendung beim Heilstättenmaterial*. *Beitr. z. klin. d. Tuberk.*, 1903, i, 325.

³ Bandelier: *Die Tuberkulindiagnostik in den Lungenheilstätten*. *Beitr. z. Klin. d. Tuberk.*, 1904, ii, 285.

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per cent., failed to react; 12 of these 37 were continued to larger doses, 4 reacting to 20 mg. and 6 more to 50 mg. Röth-Schulz¹ reports the results obtained at Beelitz Sanatorium upon a material similar to Bandelier's. Of 670 men 98.5 per cent. reacted. To 0.5 mg. 72 per cent. reacted; to 1.25 mg. 22.7 per cent. reacted; to 2.5 mg. 5.3 per cent. reacted. Of 299 women 96.3 per cent. reacted. To 0.5 mg. 35.2 per cent.; to 1.25 mg. 39.1 per cent.; to 2.5 mg. 25.6 per cent.

The Value of the Subcutaneous Tuberculin Test in Diagnosis.—From the evidence that we have so far given we are now prepared to draw the conclusion that the subcutaneous tuberculin test is broadly an index of tuberculous infection and not of tuberculous disease. We have seen that from forty to sixty per cent. of healthy adults react to the subcutaneous tuberculin test as ordinarily given and that most of those who are suspected from symptoms or physical signs of harboring a tuberculous lesion react. If, then, tuberculin discovers inactive and relatively benign tuberculous infections, of what value is it in aiding us to decide in questionable instances whether or not the individual has active disease which clinically is the only type of infection about which we are concerned? We think it must be evident that tuberculin can never answer the question categorically and the lack of appreciation of tuberculin in diagnosis has arisen because we have expected too much of it, have lacked critical discernment in the interpretation of its results and have been disappointed in its apparent indefiniteness. A reaction to tuberculin means essentially that the individual reacting has a tuberculous infection and in itself means nothing more. However, though tuberculous infection stimulates a certain degree of hypersensitivity to tuberculin, it might be that the degree of hypersen-

¹ Röth-Schulz: Über den diagnostischen Wert des alten Kochschen Tuberkulins. Beitr. z. Klin d. Tuberk., 1906, vi, 167.

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sitiveness would vary uniformly in active and inactive lesions. If such were the case the degree of tuberculin hypersensitiveness would satisfactorily divide the clinically important from the clinically unimportant infections. Krompecher¹ has shown that in animals the more virulent the infection the greater the degree of hypersensitiveness and we have already referred to Römer's studies on guinea pigs, pointing in the same direction. Certainly in man no such fixed relation exists. Hypersensitiveness does vary but we know too little about the causes of such variations to use them practically in diagnosis. All we can say is that in a general way the higher the grade of hypersensitiveness the more acute the infection. Thus severe reactions to initial small doses are more apt to be associated with active lesions than mild reactions to large or repeated doses. Unfortunately there is no dividing line in the degree of hypersensitiveness that separates sharply the active from the inactive lesions and still less the active latent from the active manifest lesions. If we employ large doses in diagnosis we will miss few clinically tuberculous cases but will likewise include most lesions that we clinically wish not to include; if we employ small doses we include less inactive lesions but immediately clinically important lesions also begin to drop out. Thus tuberculin always gives us either too much or too little and it is only by interpreting its results with this clearly in mind that anything like a just appreciation of its value can be arrived at.

We repeat that from forty to sixty per cent. of healthy adults react to tuberculin given subcutaneously and this result must be carried strictly into an estimate of its value in dealing with cases suspected clinically of having tuberculous disease. This very logical claim has, however, by

¹ Krompecher: *Recherches sur le traitement des animaux tuberculeux par la méthode de Lande* et sur la virulence des bacilles tuberculeux. *Ann. de l'Inst. Pasteur*, 1900, xiv, 723.

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no means been followed. For instance, Bandelier assumes that when symptoms and signs suggesting the existence of pulmonary tuberculosis are present a reaction to tuberculin absolutely settles the diagnosis. It is generally known that both the symptoms and signs of an early obscure tuberculous lesion are often indefinite, and as they may be simulated by a number of other diseases judgment in many instances is difficult. Indeed it is this very difficulty that has led to the use of tuberculin as an aid in arriving at a conclusion. And to be strict in our interpretation we must allow that among individuals suspected of having tuberculosis from forty to sixty per cent. will react, whether they are clinically tuberculous or not, just as from forty to sixty per cent. of healthy unsuspected individuals will react. This is what Bandelier and many others refuse to allow. To use Bandelier's own words, "The quintessence of tuberculin diagnosis is in the 'sicherstellung,' the making absolutely sure, of the diagnosis of doubtful cases." Again: "To depend on tuberculin diagnosis is to accept the most reliable method, without which an irreproachable statistic of sanatorium results cannot be reached." And still further, in speaking of the diagnosis of doubtful cases, "Tuberculin diagnosis alone can in these instances bring the desired clearing up to all concerned in an irreproachable manner." It is very difficult to see how tuberculin can do this when forty to sixty per cent. of healthy individuals react.

Evidently Bandelier's error arises from the enthusiasm which has led him to transfer to one element the impression of certainty that resides in the composite clinical picture. Of his five hundred cases all but 37 reacted, which does support the importance of the symptoms and signs that led to the admission of these patients to the sanatorium, but the reaction does not guarantee the diagnosis in each individual case. The tuberculin reaction has added another link to

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the chain of convincing evidence but has not in itself indisputably settled the diagnosis. The diagnosis is reached only by a consideration of all the evidence at hand and we are convinced that this is Bandelier's attitude, for he is conversant with Beck's statistics. The 37 cases that failed to react were in no way clinically distinguishable from those that did. They were excluded solely on the tuberculin basis. It would seem highly probable that there must have been among the reacting cases a certain number who in spite of the positive tuberculin reaction did not have active pulmonary tuberculosis.

A positive tuberculin reaction is then merely confirmative evidence and never decides with certainty an otherwise doubtful diagnosis. Indeed we feel that the caution is decidedly in place not to lay too much emphasis upon a positive reaction, for if a patient is suffering from symptoms which might be accounted for by a number of different conditions, and by applying the test we admit such uncertainty, a positive reaction does not impel the conclusion that these symptoms are due to tuberculosis. If such a large percentage of healthy individuals harbor clinically unimportant tuberculous lesions, a certain proportion of those suspected of having tuberculosis must likewise harbor them, though the symptoms that attract our attention may be due to some other disease.

A failure to react to tuberculin administered according to the method we have outlined has a more important clinical significance. With reasonable probability it excludes the presence of an active tuberculous lesion and stamps the symptoms we are investigating as not dependent upon tuberculous disease. There are certain restrictions to which this conclusion must be subjected and we refer to the consideration of the conditions under which tuberculin hypersensitiveness may be absent in spite of the presence

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of a tuberculous lesion.¹ The only one of these conditions that need seriously concern us is the unusual instance in which there is no reaction to five or ten milligrams of tuberculin in spite of the presence of a lesion that turns out to be definitely tuberculous, and in spite of the reasonable exclusion of the usual conditions obliterating tuberculin hypersensitiveness. The only explanation we can offer of such an occurrence is that the lesion is so completely cut off from the circulation that insufficient material is absorbed to stimulate a hypersensitive response and clinical interpretation usually lends support to such an explanation. But two instances have come under our own notice. A patient in the service of Dr. Halsted failed to react to tuberculin. At operation a small well-walled-off focus of tuberculous caries was found in a rib. A patient clinically with all the symptoms and physical signs of a quiescent apical pulmonary tuberculosis but without tubercle bacilli in the sputum failed to react to ten milligrams of tuberculin. It is quite probable that he might have reacted to a somewhat larger dose, since the cutaneous and conjunctival tests were both positive. We do not pretend that either 5 or 10 mg. is the dose of tuberculin to which all individuals affected with tuberculosis must react. We have discussed this point at length. We merely state that experience has shown that extremely few tuberculous cases do fail to react to these doses and while we cannot say that a negative subcutaneous tuberculin test excludes with certainty an active or clinically important tuberculous lesion, it does exclude it with the highest degree of probability.

A focal reaction, as we have previously said, is one of the most decisive and important diagnostic phenomena that we are able to observe. The difficulty is in its appreciation, for the suspected lesions that we are called upon to investigate are seldom external. The symptoms and

¹ See page 61.

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signs of a focal reaction depend upon the organ or structure involved and we shall reserve a discussion of them until we speak of the tuberculin diagnosis of special conditions.

This estimate of the value of the subcutaneous test in diagnosis is based solely upon results obtained in adults. There are no extensive figures bearing upon its use in children but experience in general has led to the conviction that in early life reactions to the subcutaneous test are far less frequent. Anatomical studies alone would lead us to predict this and the conclusion is verified by the application of the local tuberculin reactions to a large number of children. These results we will speak of later in the appropriate chapters. We call attention again to the almost uniform absence of reaction in infants. With increasing age the number of infected children grows and with it the number of those who react. The positive subcutaneous tuberculin test loses, therefore, in diagnostic significance from infancy to adult life. In children under ten years of age one would find a much smaller percentage of reactions among the healthy than has been observed among adults.

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Method of Administering the Cutaneous Tuberculin Test.—From his studies on revaccination v. Pirquet was led to the cutaneous tuberculin test. It is a specific hypersensitive reaction analogous to the local reaction observed at the point of injection in administering tuberculin subcutaneously. The test is performed as follows: The skin is cleansed with alcohol or ether and two drops of tuberculin applied about six centimeters apart. With a suitable instrument a superficial abrasion is made in the skin between the two drops and then a similar abrasion is made through each drop of tuberculin. Two drops of tuberculin

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are used to judge the uniformity of the technique, the abrasion without tuberculin as a control. The region selected for performing the test, the manner of causing the abrasion, the strength of tuberculin used and the length of time the tuberculin is allowed to remain in contact with the skin are points to be discussed.

Extensive application of the cutaneous tuberculin test has revealed the remarkable fact that the skin of different portions of the body is not equally sensitive. Schütz and Vidéky¹ have studied the differences with care. The arm is most sensitive, the thighs next and the trunk least. On account of its convenience the flexor surface of the forearm has been chiefly used, but it should be remembered that tests performed on different portions of the body are not strictly comparable.

The manner of making the abrasion is not an essential feature. It is merely necessary that the trauma be sufficient for absorption to take place. v. Pirquet has devised a borer consisting of a heavy handle with a spade-shaped platinum tip which when revolved between the fingers causes a small cup-like depression in the skin. Without practice it is difficult to produce just the right pressure to insure satisfactory absorption. A good guide is to make enough pressure so that shortly after removing the instrument a fine thread of blood can be seen curling up through the tuberculin from the base of the abrasion. Many observers scratch the skin with a needle or blood sticker. With the point of a scalpel either one or two parallel incisions may be made through the superficial layers of the skin. With a little practice the proper depth is quickly learned. The line of incision should not bleed, but to be sure of

¹Schutz and Vidéky: Ueber den Zusammenhang der exsudativen (phlyktänulären) Augenerkrankungen und der Tuberkulose nebst Erfahrungen über den Wert der kutanen und subkutanen Tuberkulin-diagnostik. Wien. klin. Wchnschr., 1908, xxi, 1285.

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sufficient absorption a few small points of blood should appear. We prefer the incision to the boring method, since it is less painful, equally if not more sensitive, permits more uniform readings, since there is no traumatic reaction, and allows a more uniform technique.

The cutaneous test is usually performed with pure tuberculin. v. Pirquet at first employed a 25-per-cent. solution but has subsequently preferred the pure. The main value of the test in diagnosis is in excluding active tuberculosis and by using pure tuberculin the absence of reaction is in this respect more certain. Attempts to obtain information of diagnostic importance by using successively increasing dilutions have, as we shall later point out, failed.

The tuberculin is allowed to remain upon the skin for from five to ten minutes after the abrasion is made. This insures, according to our observation, the maximum amount of absorption. It has been advised to protect the point of application by a vaccination shield and to allow the tuberculin to dry upon the skin. In a large series of cases we have found that by leaving the tuberculin in contact with the abrasion for ten minutes, for half an hour, for one hour, and allowing it to dry, all produce reactions within the limit of normal variation. This indicates, what we should anticipate, that absorption through the small abrasion ceases after ten minutes. As only a small amount of the tuberculin is absorbed, the size of the drop is an unimportant factor and to accurately measure it is a needless refinement. At the end of ten minutes the remaining tuberculin is gently mopped off with a bit of absorbent cotton, care being taken that no tuberculin flows upon the control. No dressing of any character is required.

The tests are inspected at the end of twenty-four hours and the points where tuberculin was applied carefully compared with the control abrasion. To the boring method the control shows a distinct traumatic reaction, consisting

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of an inflammatory areola with at times a little infiltration. This traumatic reaction makes it difficult to read mild tuberculin reactions, and if this method be employed the tuberculin areola should be five millimeters wider than the control before being called definitely positive. The reactions are usually designated as follows:

1. *Negative Reaction*: No appreciable difference between the tuberculin areas and the control.

2. *Slight Reaction*: Definite but slight redness with some infiltration.

3. *+ Reaction*: A wider area of redness with a definitely raised center.

4. *++ Reaction*: Wider area of redness with more marked infiltration than +.

5. *+++ Reaction*: Unusual redness and a wide area of infiltration. All cases which go on to vesiculation.

This is a very rough plan but the test itself is a rough one, and for practical purposes it suffices. A more accurate method is to measure the diameter of the inflammatory areola in millimeters and to express the degree of infiltration in roman numerals. Thus, I¹² is a wide area of redness with relatively slight infiltration, III²⁰ extensive redness and marked infiltration, etc.

The usual, or, as it is called, normal, tuberculin reaction begins to appear in from four to six hours, reaches its maximum in from twenty-four to forty-eight hours and then rapidly fades, although the infiltration may persist for some days. Special types of the reaction have been described as follows:

1. The *premature reaction*, characterized by a rapid course and slight intensity. It begins in from four to six hours, reaches its maximum speedily, sometimes after only ten hours, and disappears rapidly, at the latest on the second day. This type is supposed to occur in patients with manifest tuberculosis, who are not doing well.

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2. The *persisting reaction* begins like the others but reaches its maximum slowly and gradually, usually at the end of the second day and in some cases still later, the maximum persisting unchanged for a week, and often for two or three weeks.

3. The *late reaction* makes its appearance after an incubation period of over twenty-four hours and develops and recedes slowly. These two types are supposed to occur in patients with inactive lesions.

4. The *cachectic reaction* is characterized by infiltration with little or no redness. It can be better appreciated by touch than by sight. This type, as the name indicates, is common in late stages of tuberculous disease.

5. The *scrofulous reaction*: The skin about the area of reaction shows numerous small elevated nodules. Similar tuberculides may appear simultaneously upon the limbs and trunk. This type of reaction is peculiar to children and is but seldom seen in adults.

It is exceptional that the cutaneous reaction becomes vesicular and but very rarely does it become pustular or hemorrhagic. In many thousand cases we have observed but one instance of pustulation.

The Pathological Histology of the Cutaneous Tuberculin Reaction.—The cutaneous papule resulting from the absorption of tuberculin has the histological structure of a tubercle. Sections have been studied by Bandelier and Kreibich,¹ Daels² and Zieler.³ There is extensive round cell infiltration about the deeper blood vessels and giant

¹ Bandelier and Kreibich: Erfahrungen über kutane Tuberkulinimpfungen (Pirquet) bei Erwachsenen. Deutsch. med. Wchnschr., 1907, xxxiii, 1629.

² Daels: Zur Kenntnis der kutanen Impfpapeln bei der Tuberkulosediagnose nach von Pirquet. Med. Klin., 1908, iv, 58.

³ Zieler: Experimentelle Untersuchungen über tuberkulöse Veränderungen an der Haut ohne Mitwirkung von Tuberkelbazillen (toxische Tuberkulosen) und die Bedingungen ihres Entstehens. München. med. Wchnschr., 1908, iv, 1685.

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cells are frequently found. Zieler's description is as follows: "The histological changes are in the beginning little characteristic but soon nodules develop consisting of epithelioid cells and a surrounding zone of round cells which inclose a varying number of giant cells, many typically of the Langhans type. It is especially noteworthy that during the first three to five weeks these changes extend in depth and width so that the process measures about one cm. in all directions. Very characteristic in my opinion is the occurrence of these histologically typical tuberculous nodules in the course of the blood vessels and particularly the veins, whose walls are frequently infiltrated and penetrated, causing partial or complete occlusion of the vessel. These changes are very plainly and beautifully shown at some distance from the point of application, e. g., in the depth of the subcutis directly over the fascia. In the neighborhood of the point of inoculation they are, except for the large number of Langhans giant cells, less characteristic, although a partial necrosis which never occurs at a distance from it may persist for weeks. These changes gradually heal, but after three and a half months there are still epithelioid cell tubercles in the vessel walls and numerous Langhans giant cells about the point of inoculation."

The Results of the Application of the Cutaneous Tuberculin Test.—We have applied the cutaneous tuberculin test to a large and varied adult clinical material, large enough to warrant deductions of general applicability. The details of the investigation upon 1,532 patients have been previously published¹ and from the 1,000 cases analyzed in the second report the following results were obtained. We have divided the cases into six groups: non-tuberculous, doubtful, probable, incipient, moderately advanced and far ad-

¹Hamman and Wolman: The cutaneous and conjunctival tuberculin tests in the diagnosis of pulmonary tuberculosis. *Arch. Int. Med.*, May, 1909; *ibid.*, Dec., 1910.

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vanced. This division is based on a careful clinical study, without reference to the result of the tests. As tuberculous, we included cases with tubercle bacilli in the sputum, and those affording only the strongest clinical evidence of tuberculosis. Cases concerning which clinical observers might have even a slight doubt have been placed in the doubtful class, which is therefore large, in order to elicit more clearly the significance of the reactions. The probable group includes cases which most clinicians would regard as tuberculous, but for which the evidence is not absolutely convincing. The non-tuberculous group includes patients who are apparently well, or whose symptoms are demonstrably referable to some non-tuberculous cause.

| | | | |
|--------------------------|-----------|------------|-----------|
| Of 188 non-tuberculous | cases 108 | reacted=57 | per cent. |
| “ 429 doubtful | “ 386 | “ =83 | “ “ |
| “ 78 probable | “ 73 | “ =93 | “ “ |
| “ 35 incipient | “ 33 | “ =94 | “ “ |
| “ 79 moderately advanced | “ 77 | “ =97 | “ “ |
| “ 191 far advanced | “ 75 | “ =92 | “ “ |

As the doubtful cases in this classification may properly be included with the non-tuberculous and the probable with the tuberculous, we have 75 per cent. reactions in the former class and 93 per cent. in the latter.

v. Pirquet¹ among 757 children found:

| | | | |
|-------------------------------|-----------|------------|-----------|
| Of 130 clinically tuberculous | cases 113 | reacted=87 | per cent. |
| “ 115 “ doubtful | “ 56 | “ =50 | “ “ |
| “ 512 “ non-tuberculous | “ 104 | “ =20 | “ “ |

Of 124 other cases that came to autopsy:

| | | |
|-----------------------------------------------------|----|-------------|
| 64 anatomically free from tuberculosis..... | 0 | had reacted |
| 14 in whom tuberculosis was incidentally discovered | 10 | “ “ |
| 45 in whom tuberculosis caused death..... | 31 | “ “ |

¹ v. Pirquet: Kutane und konjunktivale Tuberkulinreaktion. Kraus and Levaditi: Handbuch der Technik und Methodik der Immunitätsforschung. Jena, 1908, i, 1035.

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He concludes that a positive cutaneous reaction never occurs in the absence of a tuberculous lesion; a negative reaction in general points to the absence of a tuberculous focus, but the reaction often fails in the terminal stages of the disease and may be absent when death is due to other causes.

Analyzing 988 cases according to age v. Pirquet obtains these figures:

| | |
|---------------|-----------------------|
| 0 to 3 months | 0 per cent. reactions |
| 3 " 6 " | 5 " " " |
| 6 " 12 " | 16 " " " |
| 1 " 2 years | 24 " " " |
| 2 " 4 " | 37 " " " |
| 4 " 6 " | 53 " " " |
| 6 " 10 " | 57 " " " |
| 10 " 14 " | 68 " " " |
| Over 14 " | 90 " " " |

Sperk performed the cutaneous test upon 159 infants under three months of age and none reacted.¹

Faludi tested 195 new-born infants and found that none reacted, although 126 of the mothers did react.²

Engel and Bauer performed the cutaneous test upon 288 children with the following results:³

| | | |
|-------------|-----------------------|------------------------|
| 20 children | 3 and 4 years of age: | 3 reacted=15 per cent. |
| 37 " | 5 " 6 " " " | 6 " =16 " " |
| 44 " | 7 " 8 " " " | 14 " =32 " " |
| 66 " | 9 " 10 " " " | 32 " =48 " " |
| 75 " | 11 " 12 " " " | 27 " =36 " " |
| 46 " | 13 " 14 " " " | 25 " =54 " " |

Ganghofner⁴ reports observations upon 552 children:

¹ Sperk: Cit. v. Pirquet, loc. cit., p. 119.

² Faludi: Cit. v. Pirquet, loc. cit., p. 119.

³ Engel and Bauer: Erfahrungen mit der v. Pirquet'schen Tuberkulinreaktion. Berl. klin. Wehnschr., 1907, lxiv, 1169.

⁴ Ganghofner: Ueber die Pirquetsche Tuberkulinreaktion. Wien. klin. Wehnschr., 1908, xxi, 1403.

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| | | | | Clinically Non-tuberculous | | Clinically Tuberculous | |
|----------------|----|-------|--|----------------------------|------------------|------------------------|---------|
| Ages | | | | Number | Reacted | Number | Reacted |
| Under 3 months | | | | 10 | 0=0 per cent. | | |
| 3 to 6 | " | | | 18 | 1=5 " " | | |
| 6 " | 9 | " | | 23 | 2=8 " " | 2 | 2 |
| 9 " | 12 | " | | 19 | 3=15 " " | 2 | 2 |
| 1 " | 2 | years | | 56 | 7=12 " " | 7 | 4 |
| 2 " | 3 | " | | 53 | 8=15 " " | 4 | 4 |
| 3 " | 4 | " | | 44 | 18=40 " " | 12 | 11 |
| 4 " | 5 | " | | 39 | 14=36 " " | 6 | 5 |
| 5 " | 6 | " | | 26 | 15=51 " " | 7 | 5 |
| 6 " | 7 | " | | 22 | 11=50 " " | 14 | 14 |
| 7 " | 8 | " | | 20 | 10=50 " " | 6 | 6 |
| 8 " | 9 | " | | 22 | 15=68 " " | 6 | 5 |
| 9 " | 10 | " | | 20 | 12=60 " " | 3 | 3 |
| 10 " | 11 | " | | 19 | 11=58 " " | 7 | 7 |
| 11 " | 12 | " | | 23 | 15=65 " " | 10 | 10 |
| 12 " | 13 | " | | 22 | 16=72 " " | 3 | 3 |
| 13 " | 14 | " | | 26 | 21=80 " " | 1 | 1 |
| | | | | 462 | 179=38 per cent. | 90 | 82 |

60 of the cases came to autopsy:

15 had reacted; 14 showed tuberculous lesions; in one no microscopic tuberculosis was found.

2 had doubtful reactions; neither showed tuberculosis.

43 had failed to react; in only one was tuberculosis discovered, viz., tuberculous meningitis.

Müller¹ performed the cutaneous test upon 949 children.

| | | |
|--------------|-----------------------|------------------------|
| 160 children | 0 to 3 months of age: | 13 reacted=8 per cent. |
| 158 " | 3 " 6 " " " | 11 " =7 " " |
| 137 " | 6 " 12 " " " | 16 " =12 " " |
| 67 " | 1 " 2 years " " | 15 " =22 " " |
| 82 " | 2 " 4 " " " | 25 " =31 " " |
| 57 " | 4 " 6 " " " | 21 " =37 " " |
| 139 " | 6 " 10 " " " | 50 " =36 " " |
| 149 " | 10 " 14 " " " | 80 " =54 " " |

¹ Müller: Ueber den Wert der Pirquet'schen Reaction. Arch. f. Kinderh., 1909, i, 18.

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Of the children from 1 to 14 years of age:

| | | | |
|-----|------------------------------------------------|----|----------------------|
| 71 | were clinically tuberculous..... | 43 | reacted=61 per cent. |
| 67 | “ “ suspected of having tuber- culosis..... | 49 | “ =73 “ “ |
| 359 | “ “ not tuberculous | 97 | “ =27 “ “ |

Of the 28 clinically tuberculous cases that failed to react:

| | |
|----|--------------------------------------|
| 17 | had miliary tuberculosis |
| 7 | “ tuberculous meningitis |
| 1 | “ “ peritonitis |
| 3 | “ progressing pulmonary tuberculosis |

Ninety-nine cases came to autopsy:

| | |
|----|-----------------------------------------------------------|
| 22 | had reacted and all showed tuberculous lesions |
| 77 | failed to react: 12 of these did show tuberculous lesions |
| 7 | had miliary tuberculosis |
| 3 | “ tuberculous meningitis |
| 1 | “ “ peritonitis |
| 1 | “ pulmonary tuberculosis |

Calmette, Grysez and Letulle¹ report observations made upon 1,226 children at Lille:

| | | | |
|--------------|--------------|---------|---------------|
| Under 1 year | 273 children | Reacted | 8.7 per cent. |
| 1 to 2 years | 145 “ | “ | 22.1 “ “ |
| 2 “ 5 “ | 206 “ | “ | 53.8 “ “ |
| 5 “ 15 “ | 366 “ | “ | 81.4 “ “ |
| Over 15 “ | 236 “ | “ | 87.7 “ “ |

Estimated according to the death rate for tuberculosis in Lille but 24 per cent. of these children are destined to develop manifest tuberculosis in spite of the large number of reactions. Seventy-six per cent. will certainly escape it.

The Value of the Cutaneous Tuberculin Test in Diagnosis.—From the foregoing figures a number of conclusions may obviously be drawn:

¹ Calmette, Grysez and Letulle: *Fréquence relative de l'infection bacillaire et de tuberculose. Presse méd.*, 1911, xix, 651.

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1. The cutaneous tuberculin reaction is absolutely specific just as is the subcutaneous test. A reaction never occurs in the absence of tuberculous infection and even upon gross examination the evidence of such infection is seldom missed.

2. The cutaneous reaction is always positive when a tuberculous infection is present except under certain well-defined conditions, excluding errors in technique. Those that concern us here notably are:

a.—Acute tuberculous infection such as miliary tuberculosis, tuberculous meningitis, rapidly progressing pulmonary tuberculosis.

b.—In the terminal stages of more chronic tuberculous disease.

c.—In the presence of other acute infections, particularly when they are fatal.

3. The frequency of tuberculous infection indicated by the cutaneous test rises with great rapidity from infancy to adult age. During the first year of life reactions are uncommon in clinically healthy children; at eight years forty per cent. of the children are infected; at fourteen years over sixty per cent. and at twenty-one at least eighty per cent. These figures are not absolute, they are relative only to the cutaneous test and we shall see that more delicate methods of applying tuberculin show that the actual percentage of infection is still higher.

With these simple, well-established facts in mind there is no difficulty in deducing at once the value of the cutaneous tuberculin test in diagnosis. It may be well to emphasize that the cutaneous application of tuberculin, and let us say once for all that the absorption of tuberculin from any portion of the organism stimulates a preexisting hypersensitiveness. We have already spoken in detail of this phenomenon. This stimulation is both general and

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local. If the cutaneous test is performed to-day upon the left arm, the reaction will usually be more intense if performed two weeks later upon the right arm, and many tests at first negative or doubtful become definitely positive upon a second application. Even more striking is this increased reactivity when the second test is performed upon the skin in the neighborhood of the primary test area. This local sensitization is particularly evident in repeated conjunctival instillations, as has been pointed out. What we have already said about the clinical interpretation of the subcutaneous test may be almost completely applied to the cutaneous test, except that with the latter we seldom attempt the production of focal reactions. Unquestionably slight focal changes may occur following absorption from the cutaneous abrasion, but such changes are seldom clinically appreciable. The one important exception to this statement applies to lesions of the skin itself. A focal cutaneous reaction may be elicited by applying the tuberculin directly to a suspected skin lesion and thus conclusive evidence of its tuberculous nature be obtained without the inconvenience of a general reaction. We can say but a word in passing of the extreme importance of cutaneous lesions in the diagnosis of tuberculosis in children.¹ Folliculitis, lichen scrofulosorum and erythema induratum are evident indications but of far greater importance than these because more common are the scattered tuberculides which are discovered only when carefully looked for. We in Baltimore owe to v. Pirquet the demonstration of their frequency. They are small, slightly raised, erythematous papules about pin-head in size, situated upon the trunk or more often upon the extremities, frequently with minute central white areas or depressions. Anatomically they are characteristic tubercles which form about bacilli lodged in the capillaries

¹See particularly Hamburger: *Allgemeine Pathologie und Diagnostik der Kindertuberkulose*. Leipzig, 1910.

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of the skin, the white central point being due to caseation, the depression to absorption of the necrotic material. Following a positive cutaneous test they may exhibit an inflammatory reaction zone which makes them more easily discernible than at other times.

Aside from these focal reactions a positive cutaneous tuberculin test decreases in its value as a clinical indication of tuberculous disease in direct proportion with the age up to adult life. One mathematically inclined might construct a table giving the index of value for each year, but it may be satisfactorily enough expressed by saying that a positive reaction is of considerable value in diagnosis during the first year of life, of less during the second year, of little in childhood and of none in adult life.

On the other hand, a negative reaction excludes, with definite exceptions, the presence of an active tuberculous lesion. What these exceptions are we have sufficiently set forth and harp upon them so insistently because of their extreme practical importance and of the frequency with which this importance is neglected and the test received with too simple a confidence, or unjustly abused for well-known shortcomings. If a positive cutaneous tuberculin test has no more diagnostic value than the evidence at hand compels us to conclude, may it not be that differences in the character and intensity of the reaction are important practical indications? As regards the character of the reaction, different types have been described, but their occurrence is too inconstant and the variations not sharply enough defined to be of more than occasional value, and indeed of suggestive rather than absolute value. In a general way it may be said that an intense reaction is indicative of a fresh invasion, a mild reaction of an old quiescent process. Our analyses show that there is distinctly a higher percentage of severe reactions in definitely tuberculous individuals than in healthy individuals, namely, eight and twenty-five

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per cent., respectively, but so many exceptions will be found to such a rule that it has but little practical value.

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Method of Administration of the Conjunctival Tuberculin Test.—In a discussion of v. Pirquet's report before the Berlin Medical Society¹ Wolff-Eisner stated that he had obtained reactions to tuberculin by instilling it into the conjunctival sac. The announcement was made at the time as of scientific interest, but its practical application to diagnosis was also emphasized. Quite independently of Wolff-Eisner, Calmette had conceived the same notion and published his observations shortly after Wolff-Eisner's statements were made.² In his experience Calmette then and since has used dilutions in salt solution of the washed precipitate obtained by treating old tuberculin with alcohol. Such solutions, in from one-half to two-per-cent. strengths, are marketed as tuberculin-test. As far as our experience goes, we can find no advantage in the precipitated tuberculin over the unaltered original tuberculin, which is, therefore, to be preferred on account of its simplicity and inexpensiveness. Furthermore Hamill, Carpenter and Cope³ and Smithies and Walker⁴ contend that there is great variation in the strength of the precipitated tuberculin. Apparently slight differences in the method of preparation give widely different results. It must be emphasized that solutions of precipitated tuberculin are much stronger than solutions of unaltered old tuberculin, the former being ap-

¹ Discussion on tuberculin. Berl. klin. Wschnschr., 1907, xlv, 70.

² Calmette: Un nouveau procédé de diagnostic de la tuberculose chez l'homme. L'ophthalmo-réaction à la tuberculin. Presse méd., 1907, xv, 388.

³ Hamill, Carpenter and Cope: A comparison of the von Pirquet, Calmette and Moro tuberculin tests and their diagnostic value. Arch. Int. Met., 1908, ii, 405.

⁴ Smithies and Walker: The conjunctival tuberculin reaction as a means of diagnosis and control. Jour. Am. Med. Assn., 1909, lii, 25.

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proximately ten times as strong as the latter. Mitulescu has estimated that a 1 to 10,000 solution of Höchst's purified tuberculin is equal to a 1 to 1,000 solution of the tuberculin sent out by the Pasteur Institute at Lille. Damask¹ has shown that the Pasteur Institute tuberculin is about two and a half times as strong as a 1-per-cent. solution of Höchst's old tuberculin. The Höchst's purified tuberculin, which was extensively used in Germany, was later withdrawn on account of the numerous severe reactions following its use. We invariably employ a 1-per-cent. solution of old tuberculin in normal salt solution. For these tests, as for the subcutaneous test, a standardized tuberculin should be employed.

The technique of the test is extremely simple. After carefully inspecting the conjunctivæ and the eyeballs to ascertain if there is any evidence of disease and if the conjunctivæ are strictly comparable in color, the lower lid is drawn forward so as to form a little pouch, the patient is instructed to rotate the eyeball outward and from an ordinary eye-dropper one drop of a 1-per-cent. dilution of tuberculin is touched to the lid at the inner canthus. When the test is skilfully performed there is rarely lacrimation enough for a tear to escape upon the cheek. If lacrimation is abundant the value of the test is impaired. It is useless to attempt to give the test to unwilling or weeping children. At the end of twenty-four hours the conjunctivæ are inspected and carefully compared. In mild reactions the inner canthus is the seat of the most marked change. For a reaction to be positive the difference between the two conjunctivæ should be easily perceived and no doubtful reactions should ever be classed as positive. It is far better to err in the other direction. It is convenient to classify the positive reactions according to intensity as:

¹ Damask: Ueber Bedeutung der Ophthalmoreaktion auf Tuberkulin. Wien. klin. Wchnschr., 1908, xxi, 121.

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| | | | |
|---|---|-----------|------------------------------------------------------------------------------------|
| + | + | Reaction: | Definite palpebral redness. |
| + | + | “ | More marked palpebral redness with secretion. |
| + | + | + | “ Palpebral and bulbar redness with subjective symptoms and well-marked secretion. |

The only technical refinement that can add to the comparative value of the test is to use an accurately measured drop. For practical purposes small variations in the size of the drop are a negligible factor, but for those wishing to use such precision the capillary pipette devised by Baldwin is indispensable.¹

After the instillation, should the reaction be positive, the conjunctiva begins to redden at the end of six to eight hours, reaches its maximum in twenty-four to thirty-six hours and rapidly subsides, in mild reactions the inflammation being over in two to three days, in severe reactions in four to six days. Evanescient reactions coming on in from four to eight hours and subsiding in from twelve to twenty-four hours have been described but have no importance in diagnosis. Only exceptionally are reactions so severe that redness persists longer than six days. Should the instillation of a drop of a 1-per-cent. solution of tuberculin be followed by no reaction, it may be desirable to extend the investigation. The opposite eye is then chosen for the second test. We have a rough measure of the patient's tolerance for tuberculin through his failure to react to the 1-per-cent. dilution, and a drop of a 5-per-cent. dilution may safely be chosen for the second instillation. These doses are selected because in our experience they are free from danger and at the same time give the greatest amount of desired information.

¹ Baldwin: The ophthalmo-tuberculin diagnostic tests. Jour. Am. Med. Assn., 1907, lxix, 1969.

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The question of the disadvantage and the real dangers of the conjunctival test demands serious consideration. Such consideration it shall receive in the chapter devoted to the dangers and untoward effects of tuberculin administration. We wish only to state here that our own experience has led us to believe that the serious results which have followed conjunctival tuberculin instillations can with proper precaution be minimized, if not completely avoided, and that the risk run is not great enough to force the abandonment of a procedure which has proved itself of such great value in diagnosis. We emphasize, however, the extreme importance of proper precaution and enumerate a number of conditions that must be carefully considered in carrying out the test.

1. The conjunctival test should never be repeated in the same conjunctiva. Such repetitions are dangerous and the information they afford is of no clinical value. We have repeatedly spoken of the sensitizing action of tuberculin, and in no position is the local stimulation so well illustrated as in the conjunctiva. We refer to the experiments of Rosenau and Vaughan and the interpretation of the results there given. The reactions to second instillations are often alarmingly severe. The value of the conjunctival test in diagnosis rests upon the relative infrequency of reaction among healthy individuals, and utilization of reactions depending upon local sensitization makes the test practically equivalent to the cutaneous test. The sensitizing effect of a conjunctival instillation becomes apparent in from three to four days, and reaches its maximum toward the end of the second week. It persists at a fairly high level for three months and then gradually subsides. It is uncommon to obtain a positive reaction to a second instillation of a 1-per-cent. solution into the same conjunctiva given over six months after the first instillation had been negative. In the small number of instances in which such second instilla-

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tions were made a year after the primary negative test we have never obtained a positive reaction. This leads us to believe that the sensitization is completely lost after twelve months. These statements are impressions rather than legitimate conclusions. The number of cases reinstalled has been very small. As far as we know, the question of the duration of the local sensitization has never been systematically worked out.

2. A solution stronger than 1 per cent. original tuberculin should never be used for the first instillation. It is uncommon to have intense reactions to this strength, while weaker dilutions impair the value of the test.

3. Any existing inflammatory disease of the eye is an absolute contraindication to the test. A history of previous inflammatory disease, especially of phlyctenular conjunctivitis, is likewise a contraindication.

4. The test should not be performed in the presence of severe conjunctivitis. The mild conjunctival inflammation so frequently associated with slight blepharitis marginalis is no absolute contraindication.

5. The test should not be given to manifestly scrofulous children, as they so frequently react violently to tuberculin. The presence of conjunctivitis or eczema about the eyelids, so common in these children, is an absolute contraindication to the test.

6. Skin diseases situated upon the face, near the eye, especially when these are suspected of being tuberculous, prohibit the application of the test.

7. Many of the untoward results of the conjunctival test have been reported in the aged. Impaired corneal nutrition is common in advanced years, and the risk of corneal ulceration after slight trauma or irritation is increased. It is safest not to give the test to elderly individuals and particularly not to arteriosclerotics.

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Tuberculin Test.—We cannot apply a uniform interpretation to the results of the conjunctival test since widely different strengths, single and two instillations, and repetitions in the same conjunctiva have been used. Unless details in reference to these particulars accompany the report, the results are useless for our purpose. We have published the results of our administration of the test to 1,518 individuals, nearly all adults, only a few children being included in the number. The test was performed by instilling a drop of a 1-per-cent. solution of original tuberculin into one conjunctival sac, and to a number of the individuals negative to this dilution a drop of a 5-per-cent. solution into the opposite eye. The cases are classified upon a clinical basis into six groups.

| | Number. | Reacted to 1 per Cent. | Reacted to 5 per Cent. |
|---------------------------------|---------|---------------------------|---------------------------|
| 1. Non-tuberculous | 251 | 5 = 2 | 10 out of 163 = 6 |
| 2. Doubtful | 617 | 87 = 14 | 85 " " 373 = 34 |
| 3. Probable | 149 | 55 = 37 | 37 " " 71 = 70 |
| 4. First stage pulm. tuber..... | 63 | 38 = 60 | 6 " " 18 = 73 |
| 5. Second stage pulm. tuber... | 168 | 124 = 74 | 12 " " 19 = 98 |
| 6. Third stage pulm. tuber..... | 270 | 183 = 68 | 32 " " 62 = 84 |

As in the cutaneous test, we may roughly regard the doubtful cases as clinically non-tuberculous, the probable as definitely tuberculous, giving:

Of 968 non-tuberculous patients, 94, or 9.7 per cent., react to the 1 per cent. conjunctival test.

Of 650 tuberculous patients, 400, or 61.5 per cent., react to the 1 per cent. conjunctival test.

Of 968 non-tuberculous patients, 25 per cent. react to the 5 per cent. conjunctival test.

Of 650 tuberculous patients, 81 per cent. react to the 5 per cent. conjunctival test.

The method of arriving at the percentage of reactions to the 5 per cent. is as follows: Allow, as an example, that 300 patients receive the 1-per-cent. instillation and of this number 100 react; of the 200 negative cases only 100 return

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for the 5-per-cent. instillation, and of this number 50 react. It is approximately safe to assume that, if 50 of the 100 patients that returned reacted, 50 of the other 100 patients who did not return would also have reacted, making a total of 100 reactions to the 5 per cent. among the 200 that did not react to the 1 per cent. It is further certain that the 100 patients reacting to the 1 per cent. would have reacted to the 5 per cent. had this test been given, which makes a total of 200 reactions to the 5 per cent. out of the 300 cases, or 67 per cent.

Baldwin¹ employed a 1-3-per-cent. and a 1-2-per-cent. solution of alcohol-precipitated and washed tuberculin. The product was sent in sterilized sealed tubes, with a capillary dropper graduated to 0.25 c. c., to numerous clinicians, and from their reports the tables are prepared. Eight hundred and eighty-seven individuals received the test, in 190 of whom a second instillation was made in the opposite eye, and 10 in the same eye—a total of 1,087 instillations.

The accompanying table gives the result:

| Pulmonary Tuberculosis | Cases | React- ed Pos- itively. | Per Cent. | | Cases | React- ed Pos- itively. | Per Cent. |
|---------------------------------------------------------------------------------|-------|-------------------------------|--------------|------------------------------------------------|-------|-------------------------------|--------------|
| Stage I (Incipient): | | | | Suspected tuberculo- sis, pulmonary | 219 | 73 | 33.3 |
| Tubercle bacilli demon- strated | 33* | 20 | 60.0 | Other forms | 46 | 22 | 47.8 |
| Tubercle bacilli not demon- strated | 49 | 35 | 71.4 | | | | |
| | 82 | 55 | | | | | |
| Stage II (Moderately Ad- vanced): Tubercle bacilli demonstrated | 96† | 76 | 79.2 | Other Diseases | 127 | 19 | 14.1 |
| Tubercle bacilli not demon- strated | 22‡ | 13 | 59.1 | Healthy (unsuspected) | 185 | 34 | 18.3 |
| | 118 | 89 | 75.0 | | | | |
| Stage III (Far Advanced) . . | 36 | 18 | | | | | |
| Clin. healed | 24 | 17 | | | | | |
| Other forms of tuberculosis . | 50** | 39 | 78.0 | | | | |
| Total | 310 | 218 | 70.0 | | | | |

*Nine were under tuberculin treatment and failed to react.

†Nineteen were under tuberculin treatment, of whom ten reacted positively.

‡One was under tuberculin treatment and failed to react.

**Eight were under tuberculin treatment, of whom one reacted.

¹ Baldwin: Conclusions from 1,087 conjunctival tuberculin tests by a uni-
form method. Sixth International Congress on Tuberculosis, 1908, i, pt. i, 487.

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Baldwin makes these comments upon the figures: "In reviewing the percentages in Table I, it is apparent that a considerably greater number of pulmonary cases reacted in the moderately advanced class than in the incipient, while in the far-advanced the number was less. It is probable that the patients forming the moderately advanced class, being taken from sanatoriums in the greater part, were in better condition than the hospital cases tested by Wolff-Eisner, who found a decreased percentage of reactions with the advance of the disease. The influence of tuberculin treatment in lowering the sensitiveness of the conjunctiva brought down the percentage of reactions appreciably. It is also noteworthy that fully 70 per cent. of persons healed in the clinical sense from two to thirty years reacted positively. The chief interest relates to the clinically incipient (71.4 per cent., positive) and suspected cases (33.3 per cent., positive), where the test would be expected to assist in diagnosis. The results fall considerably short of the requirements for an ideal diagnostic method in suspected tuberculosis, though relatively good in confirmation of the clinically tuberculous cases. The percentage of supposedly healthy and non-tuberculous diseases reacting positively closely accords with that found by Wolff-Eisner and Petit in a larger number of cases."

Calmette reports observations upon 6,303 individuals collected by a number of observers.¹ He does not state definitely the method employed, but it was probably a single instillation of a 1-per-cent. solution of his purified tuberculin.

| | | | |
|---------------------------------------------|-----------------|--------|-----------|
| Of 2,894 clin. tuberculous individuals..... | 2,664 reacted = | 92 | per cent. |
| Of 1,081 individuals clin. susp. of having | | | |
| tuberculosis | 616 | “ = 57 | “ |

¹ Calmette. Sur l'emploi des réactions cutanées et conjunctivales à la tuberculin (cuti-et ophthalmo-réactions) dans le diagnostic des infections tuberculeuses. Sixth International Congress on Tuberculosis, 1908, i, pt. i, 452.

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Of 2,328 individuals clin. free from tuberculosis..... 391 reacted = 16.8 per cent.

Further, of 55 unsuspected individuals who reacted to the test and later came to autopsy 49 showed macroscopic tuberculous lesions.

The following results are abstracted from Smithies and Walker.¹ The number of cases they themselves report is small, but they give valuable summaries from the literature. In their own work they use a 1-per-cent. solution of precipitated tuberculin.

1. Definitely tuberculous cases:
 - a. A summary of 1,554 cases in all stages of the disease, collected from the German literature, gives 86 per cent. reactions.
 - b. A summary of 14,800 similar cases, from the French literature, gives 93 per cent. reactions.
 - c. Personal observations: 151 cases of tuberculosis, 79 per cent. reacted.
15 cases incipient pulmonary tuberculosis, 100 per cent. reacted.
20 cases bone tuberculosis, 80 per cent. reacted.
74 cases moderately advanced pulmonary tuberculosis, 75.6 per cent. reacted.
42 cases advanced pulmonary tuberculosis, including moribund cases, 59.5 per cent. reacted.
2. Doubtful cases:
 - a. Of 476 cases collected from German literature, 51 per cent. reacted.
 - b. Of 273 cases collected from French literature, 64.5 per cent. reacted.
 - c. Of 13 personal observations, 69 per cent. reacted.
3. Individuals apparently well:
 - a. Of 1,379 cases collected from German literature, 9.9 per cent. reactions.
 - b. Calmette and Petit, from a large material, both give about 18 per cent. reactions.
 - c. Of 205 personal observations, 6.8 per cent. reactions.
Of 76 apparently healthy young men only 2 reacted, and in both of these there were fairly well-marked signs of tuberculosis.

¹ Smithies and Walker: Ocular tuberculin reaction. Jour. Am. Med. Assn., 1909, lii, 25.

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It will be noticed that the percentages of reactions from the French literature are in each case higher than those from the German. Smithies and Walker justly ascribe this to differences in the strength of the tuberculin used. The French observers mainly use the 1-per-cent. and 2-per-cent. solutions of precipitated tuberculin, the German dilutions of from 0.25-per-cent. to 4-per-cent. old tuberculin and most commonly a 1-per-cent. dilution.

Engelbach and Shankland¹ do not state what tuberculin they employ but one gets the impression that it was a 1-per-cent. precipitated tuberculin.

Their results, from a study of the literature and of their own observations, are these:

I. Positive Tuberculosis:

| | | | | |
|---------------------------------------|--------------|--------|------------------|---|
| Observations of 30 different authors. | 1,572 cases, | 86 | p. c. reactions. | |
| Schraeder and Kaufman..... | 971 | " 85.5 | " | " |
| Engelbach and Shankland..... | 70 | " 74 | " | " |

II. Suspected Tuberculosis:

| | | | | |
|---------------------------------|-----|------|---|---|
| Observations of 22 authors..... | 642 | " 48 | " | " |
| Schraeder and Kaufman..... | 284 | " 51 | " | " |
| Engelbach and Shankland..... | 190 | " 40 | " | " |

III. Other Diseases:

| | | | | |
|---------------------------------|-----|------|---|---|
| Observations of 19 authors..... | 932 | " 17 | " | " |
| Schraeder and Kaufman..... | 627 | " 13 | " | " |
| Engelbach and Shankland..... | 517 | " 24 | " | " |

IV. Clinically Normal:

| | | | | |
|--------------------------------|-----|--------|---|---|
| Observations of 8 authors..... | 351 | " 11 | " | " |
| Engelbach and Shankland..... | 79 | " 25.5 | " | " |

Wolff-Eisner speaks of the thousands of observations he has made, but as far as we know he has never published a detailed statistical study of his material. His published results are as follows:²

¹ Engelbach and Shankland: The diagnostic value of the cutaneous and conjunctival tuberculin reactions. Jour. Am. Med. Assn., 1909, lii, 37.

² Wolff-Eisner: Frühdiagnose und Tuberkulose-Immunität. 2nd edition. Würzburg, 1909, 174.

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- I. Tuberculosis: First stage pulmonary tuberculosis, 67 cases, reactions 50 = 75 per cent.
 Second stage pulmonary tuberculosis, 72 cases, reactions 45 = 62.5 per cent.
 Third stage pulmonary tuberculosis, 97 cases, reactions 31 = 32 per cent.
- II. Healthy Individuals, 656 cases, reactions 88 = 13.4 per cent.
- III. Suspected Individuals, 74 cases, reactions 37 = 50 per cent.

For facilitating a rapid oversight the following table of percentages is prepared:

| | WOLFF-EISNER | CAL- METTE | BALD- WIN | SMITHIES AND WALKER | | | ENGELBACH AND SHANKLAND | | SCHRAEDER AND KAUFMAN | HAMMAN AND WOLMAN | |
|----------------------------------|--------------|---------------|--------------|---------------------------|--------|---------------|-------------------------------|---------------|--------------------------|-------------------------|----------------|
| | | | | Literature | | Per- sonal | Litera- ture | Per- sonal | | 1 per Cent. | 5 per Cent. |
| | | | | Ger- man | French | | | | | | |
| Clinically non- tuberculous . | 13 | 17 | 17 | 10 | 18 | 7 | 17 | 25 | 13 | 10 | 25 |
| Clinically suspected . . . | 50 | 57 | 36 | 51 | 64 | 69 | 48 | 40 | 51 | 37 | 70 |
| Clinically tuberculous . | 53 | 92 | 70 | 86 | 93 | 79 | 86 | 74 | 86 | 69 | 84 |
| Pulmonary Tuberculosis | | | | | | | | | | | |
| I Stage . . . | 75 | .. | 67 | .. | .. | 100 | .. | .. | .. | 60 | 73 |
| II Stage . . . | 62 | .. | 75 | .. | .. | 76 | .. | .. | .. | 74 | 98 |
| III Stage . . . | 32 | .. | 58 | .. | .. | 59 | .. | .. | .. | 68 | 84 |
| Tuberculosis, Other Organs | .. | .. | 78 | .. | .. | 80 | .. | .. | .. | .. | .. |

The Value of the Conjunctival Tuberculin Test in Diagnosis.—There is not the same accord in the results of the application of the conjunctival tuberculin test that there is in those of the cutaneous test. Among the clinically non-tuberculous the reactions vary from two per hundred to twenty-five per hundred, among the clinically tuberculous from fifty-three to ninety-three per hundred. The variation depends on the method of applying the test and on the material upon which it is applied. Taking the results of a single instillation, the number of reactions will vary with the strength of the solution employed. We have noted the

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difference in the strength of the tuberculin used by numerous observers and a comparison of the results of the analysis of the German and French literature by Smithies and Walker shows the relative results very strikingly. A similar comparison may be made between the figures of Calmette, who has employed a 1-per-cent. solution of purified tuberculin, and our own, obtained by using a 1-per-cent. dilution of old tuberculin. To weak dilutions of tuberculin few clinically non-tuberculous individuals react, but only a little over two-thirds of the definitely tuberculous react, whereas to more concentrated dilutions nearly all of the tuberculous are positive, but a proportionally large number of the non-tuberculous react. In determining whether weaker or stronger dilutions are to be employed in practice, two considerations must guide us:

1. The strength of the solution must be kept within the limits of safety.

2. Within the limits of safety that strength should be employed which gives the most valuable clinical information.

The French observers, notably Calmette, Petit and Lapersonne, have published sufficiently extensive material to establish that the 1-per-cent. purified tuberculin prepared under Calmette's direction is, when used with care, devoid of danger. Calmette reports that in 6,303 tests the only complications noted were phlyctenular keratitis in three instances, severe conjunctivitis in twenty, and reactions prolonged beyond three weeks in seventy-two. In no instance did a permanent ocular lesion or visual defect follow. Baldwin, who has used a 1-2-per-cent. solution of precipitated tuberculin prepared by himself, reports no untoward results in 1,087 tests. It is to be presumed then that a 1-per-cent. dilution of old tuberculin, which is not as strong as the 1-per-cent. solution of precipitated tuberculin, is even less to be feared. That its application is safe

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the experience of Wolff-Eisner, Teichman, Hamman and Wolman and many other observers attests. The numerous severe reactions following the use of Höchst's purified tuberculin, which was on this account subsequently withdrawn, are evidence that dilutions stronger than 1-per-cent. purified tuberculin are not free from danger and are to be avoided. While, therefore, the 1-per-cent. dilution of old tuberculin is to be preferred to the 1-per-cent. solution of precipitated tuberculin on account of its greater safety, the advantage in this direction is not sufficient to establish its superiority, for the increased danger accompanying the use of the purified tuberculin is by no means sufficient to counterbalance possible advantages it may possess. In order to consistently advocate a preference for the 1-per-cent. old tuberculin it must be further shown that the clinical evidence it affords is more valuable than the information obtained by using the 1-per-cent. precipitated tuberculin.

That such an advantage exists we are fully convinced. In discussing the point we stumble again upon the fundamental question of the relation of tuberculin hypersensitiveness to tuberculous infection which we have previously considered. All tuberculous infections, whether clinically important or unimportant, bestow tuberculin hypersensitiveness at least temporarily upon the infected individual. Unfortunately, the degree of hypersensitiveness does not vary uniformly with the clinical import of the infection. While as a general rule extensive and active lesions are accompanied by a high degree of reactivity to tuberculin and insignificant and quiescent lesions by but slight hypersensitiveness, the dividing line is neither sharp nor constant. The exceptions are almost as important as the rule, for frequently latent active or inactive infections give rise to a high reacting power and manifest lesions to unexpectedly low hypersensitiveness. If we make the tuberculin

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test very delicate so as to reveal nearly all infections, clinically it has value only in excluding the presence of tuberculous disease; if we apply a coarser test we obtain few reactions among the clinically non-tuberculous, but at once lose from the positive side many manifestly tuberculous individuals. It seems clear that any tuberculin test must give either negative or positive information, that it cannot give either with certainty, and can never give both. We have pointed out that the value of the subcutaneous and of the cutaneous tests is almost entirely upon the negative side, namely, in excluding tuberculosis, and that a positive reaction to either is relatively unimportant as an indication of the presence of clinical tuberculosis. From the statistics that we have quoted it is evident that we can in a measure make what we will of the conjunctival test. By using strong dilutions we obtain reactions in nearly all clinically tuberculous cases, but so many healthy and merely suspected individuals react that the value of the test as an indication of tuberculous disease is seriously impaired. In fact the test has more value in excluding tuberculous disease than in affirming its presence. By using weak dilutions we obtain few reactions among healthy individuals, but also a large number of the clinically tuberculous likewise fail to react. Under these conditions the test loses all value in excluding tuberculosis, but when positive is strong confirmatory evidence of its presence. What then shall we ask of the conjunctival test? Undoubtedly its single claim upon our interest is in its indication of the existence of clinical tuberculosis. We have in the cutaneous test a simple and more accurate means of excluding the presence of tuberculous disease and it is superfluous to add the evidence of the conjunctival test to the negative side. It is for these reasons particularly that we urge so strongly the superior value of the conjunctival test performed with the 1-per-cent. old tuberculin. If no reaction follows the

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test we may gain further information by then instilling a drop of a 5-per-cent. dilution into the opposite conjunctival sac. As our figures indicate, this second test has more negative than positive value.

The second factor in importance in estimating the value of the conjunctival test in diagnosis is the rough classification that has of necessity been adopted. We have emphasized that the groups are clinical divisions and not only accept but eagerly meet the objection that such a standard is open to evident sources of error. The opinions of different clinicians vary widely in respect to individual cases; no two would group them exactly alike. This is true not only in the classification of definite instances of pulmonary tuberculosis but more particularly in deciding between doubtful and early cases of the disease. Statistics have been gathered principally among pulmonary cases. We shall return to this matter in speaking of the value of tuberculin in the diagnosis of pulmonary tuberculosis and merely point to it here as of great importance in this connection. In our own series we have paid particular attention to the classification and have divided them as accurately as can be done upon a clinical basis. Among the cases which present no features upon which a suspicion of pulmonary tuberculosis can rest we obtained but 2 per cent. of reactions. This we think is a more accurate estimate for healthy individuals than from ten to twenty-five per cent., which appears in the table. In our doubtful group we have included individuals with symptoms or physical signs which do not definitely, but still might, depend upon tuberculous disease. From such details as accompany other reports we are led to believe that our figures can best be compared with them by including these instances as clinically non-tuberculous. Of seventy observations upon healthy college students Engelbach and Shankland obtained 25 per cent. reactions. Smithies and Walker obtained only two reactions

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among 76 healthy students and in both of these there were fairly well-marked signs of tuberculosis. Vaughan in 110 students obtained 6 reactions. These authors used a solution of purified tuberculin.

Among the definitely tuberculous the number of reactions largely depends upon the criterion for admission to the incipient group and the number of far-advanced cases included. The occurrence of the reaction in early pulmonary tuberculosis has been the subject of a bitter polemic between Wolff-Eisner and Roepke. The former finds that the largest percentage of reactions occurs in the incipient group, the smallest in the far advanced; the latter that early cases but rarely react, while the highest proportion of reactions occurs in the far-advanced group. Wolff-Eisner has worked with hospital patients, Roepke with sanatorium patients. Wolff-Eisner assails Roepke's diagnosis, pointing out that he includes numerous doubtful cases in the incipient group. Roepke retorts that Wolff-Eisner fails to diagnose early cases and obtains so small a number of reactions in the far-advanced group because he includes moribund cases. To reach unquestionable results only cases with tubercle bacilli in the sputum should be used.

Among our patients 300 had tubercle bacilli in the sputum and 219 reacted = 73 per cent.

| | | | |
|---------|----------|--------------|------------------|
| I stage | 30 cases | 20 reactions | = 66 per cent. |
| II | " 101 | " 76 | " = 75 per cent. |
| III | " 169 | " 123 | " = 72 per cent. |

These figures do not differ materially from those obtained for the total number.

The reduced percentage of reactions in the advanced group depends upon the failure of rapidly advancing and moribund cases to react.

From the results quoted it is evident that the value of the conjunctival test with 1-per-cent. old tuberculin is main-

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ly in indicating the presence of clinical tuberculosis. Too many merely suspicious cases react, individuals who have not at the time and do not later develop manifest tuberculous disease, to support Wolff-Eisner's contention that a positive reaction occurs only in the presence of active tuberculosis. Still it does point strongly toward its presence, and when supported by other indications is valuable confirmatory evidence. In this respect its value is the opposite of that of the subcutaneous and cutaneous tests. A negative conjunctival reaction, on the other hand, has no value in excluding the presence of manifest tuberculous disease since so many definitely tuberculous individuals fail to react. The 5-per-cent. tuberculin conjunctival test has as much value in excluding as in establishing the presence of clinical tuberculosis. However, positively it has far less value than the 1-per-cent. test, and negatively does not approach the certainty of the subcutaneous or cutaneous test. It is, therefore, of quite secondary importance when compared with these.

Since so little dependence is to be placed upon a negative 1-per-cent. conjunctival test, it is not necessary to emphasize the special conditions under which a manifestly tuberculous individual may fail to react. They are the same as those which influence general tuberculin hypersensitiveness and have been repeatedly discussed.

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Method of Administration of the Percutaneous Tuberculin Test.—Shortly after the introduction of the cutaneous tuberculin reaction Moro and Doganoff¹ showed that a specific reaction follows the rubbing into the skin of tuberculin suspended in an ointment base. The procedure was

¹ Moro and Doganoff: Zur Pathogenese gewisser Integumentveränderungen bei Skrofulose. Wien. Klin. Wchnschr., 1907, xx, 933.

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further elaborated by Moro to be used as a general diagnostic method.¹ The ointment is prepared by thoroughly mixing equal parts of old tuberculin and lanolin previously heated to from 20° to 30° C. Moro's directions are to mix 5 c. c. of tuberculin with 5 grams of lanolin. As 5 c. c. of tuberculin weighs approximately 6 grams, the preparation is really a 60-per-cent. ointment. Ten grams of the ointment is enough for 100 tests. Although the ointment quickly darkens, it retains its potency for many months if preserved in a cold, dark place. To perform the test, a piece of the ointment as large as a pea is thoroughly rubbed with the finger for one minute over an area of skin measuring about 5 cm. in diameter. Preparations of the ointment are marketed in appropriately sized tubes. Moro selects the upper part of the abdomen or the skin about the nipple as the most satisfactory region for the application of the test. He says the forearm is not to be used. Some have advised that the physician performing the test protect his finger with a rubber cot, but apparently there is little danger of a reaction occurring upon the palmar surface of the hand. If the reaction is positive, in from 12 to 48 hours an efflorescence of papules occurs upon the anointed area of skin and frequently upon the skin immediately surrounding. The reaction is usually well marked at the end of twenty-four hours, and reaches its height in forty-eight hours. Its appearance may be delayed until the third or fourth day, and it is said even until the sixth day. The papules are slightly elevated upon a hyperemic base and vary in size from pin-head to areas of infiltration several centimeters in diameter. The efflorescence has the appearance characteristic of lichen scrofulosorum. It sub-

¹ Moro: Ueber eine diagnostische verwertbare Reaktion der Haut auf Einreibung mit Tuberkulinsalbe. München. med. Wehnschr., 1908, lv, 216.

For a full consideration of the test see Moro: Klinische Ergebnisse der perkutanen Tuberkulin-reaktion. Beitr. z. Klin. d. Tuberk., 1909, xii, 207.

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sides in from five to ten days. Moro has described these grades of reactions:

1. Mild reaction: In from 24 to 48 hours a few (1 to 10) scattered papules 1 to 3 mm. in diameter appear. The papules disappear in a few days without having occasioned itching.

2. Moderate reaction: Within 24 hours numerous (50 or more), partly discrete, partly confluent nodules appear, measuring 1 to 3 mm. in diameter. The surrounding skin is often reddened and there is usually well-marked itching. The eruption remains unaltered for several days and very gradually disappears.

3. Severe reaction: Numerous large, intensely red papules or vesicles up to 8 mm. in diameter appear upon an intensely reddened base. Often papules are scattered upon the surrounding skin. There is marked itching. In a few days the papules dry up but the skin remains red and scales. Pigmentation may persist for weeks.

There are no contraindications to the use of the Moro test unless we wish to consider such the very severe reactions which occasionally occur in scrofulous children.

Moro describes the following unusual types of reaction:

1. Disseminated reaction of the skin at a distance from the point of application of the ointment.

This type may accompany severe reactions. Papules appear not only about the reacting area but often at a distance from it and may occur upon the extremities.

2. Localized reaction of the skin at a distance from the point of application. These he divides into three classes:

- a. The symmetrical reaction. The reaction is accompanied by the appearance of papules upon the skin on the other side of the body in an exactly symmetrical position.

- b. The dislocated reaction. Only a few papules appear over the area of application, while a circumscribed follicular exanthem occurs in a neighboring portion of the skin.

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c. Half-sided, girdle-formed associated reaction of the skin.

3. Consecutive lichen scrofulosorum at the seat of reaction. The eruption appears as the original reaction fades and persists for several weeks.

4. Consecutive general exanthem. Noted in five cases. The exanthem was twice scarlatiniform, once morbilliform, once a general evanescent erythema, once purpuric with associated erythema nodosum.

The Results of the Use of the Percutaneous Tuberculin Test.—Moro¹ has published the results of the test applied to 1,034 children:

| | | | |
|-----------------------------------|-----|-----------------|-----------|
| Manifestly tuberculous..... | 96 | Reacted 79 = 83 | per cent. |
| Serofulous | 82 | " 71 = 87 | " |
| Tuberculosis suspected..... | 450 | " 330 = 73.5 | " |
| Clinically tuberculosis-free..... | 406 | " 56 = 12.5 | " |

The 17 negative cases among the definitely tuberculous were:

- 9 instances of miliary and meningeal tuberculosis.
- 2 instances of bone tuberculosis.
- 1 six months old infant.
- 1 half year old cachectic child with bronchial gland tuberculosis.
- 1 ten year old girl with tuberculous peritonitis.
- 1 eleven and a half year old child.
- 1 three and a half year old child, who some time later died of generalized tuberculosis.

Forty-four cases came to autopsy:

No tuberculosis found at autopsy, 23 instances; reacted 0.

Definite tuberculosis found at autopsy, 21 instances; reacted 14.

The 7 cases of definite tuberculosis that failed to react comprised 3 of tuberculous meningitis, 1 of miliary tuberculosis, 2 of generalized tuberculosis, and one in which the tuberculous lesion was an incidental finding, an old completely calcified mesenteric lymph gland.

¹ Moro: Ueber eine diagnostische verwertbare Reaktion der Haut auf Einreibung mit Tuberkulinsalbe. München. med. Wehnschr., 1908, lv, 216.

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Arranged according to age, Moro's results are as follows:

| | | |
|----------------|--------------------------|----|
| 0 to 3 months. | Percentage of reactions, | 0 |
| 3 " 6 " | " " " | 3 |
| 6 " 12 " | " " " | 27 |
| 1 " 2 years. | " " " | 26 |
| 2 " 4 " | " " " | 35 |
| 4 " 6 " | " " " | 41 |
| 6 " 10 " | " " " | 50 |
| 10 " 14 " | " " " | 60 |

Wetzell¹ has observations upon 140 adults:

| | | | | |
|--------------------------------------|----------|---------|---------|-----------|
| Pulmonary tuberculosis: First stage, | 6 cases. | Reacted | 5 = 83 | per cent. |
| Second stage, | 10 " | " | 8 = 80 | " |
| Third stage, | 9 " | " | 3 = 33 | " |
| Suspected tuberculosis..... | 13 " | " | 11 = 85 | " |
| Not tuberculosis | 102 " | " | 71 = 70 | " |

The negative case in the I stage had leukemia. The two negative cases in the II stage were old women 75 and 81 years old, respectively.

Bullinger² reports tests made upon 84 adults:

Clinically pulmonary tuberculosis, first and second stage, 19 cases. Reaction 15 = 80 per cent.
 Clinically pulmonary tuberculosis, third stage, 6 cases. Reaction 1 = 17 per cent.
 Clinically suspected tuberculosis, 48 cases. Reaction 35 = 73 per cent.
 Not tuberculosis, 11 cases. Reaction 1 = 9 per cent.

One of the negative cases in the first and second group was found at autopsy to have carcinoma, and not tuberculosis.

Patterson³ has studied the reaction in 171 adults:

¹ Wetzell: Beiträge zur perkutanen Tuberkulinreaktion nach Moro. Beitr. z. Klin. d. Tuberk., 1908, xi, 271.

² Bullinger: Ueber die Morosche Salbenreaktion. München. med. Wehnschr., 1909, lvi, 1325.

³ Patterson: The Moro and v. Pirquet tuberculin reactions. Arch. Int. Med., 1909, iii, 299.

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| | | |
|-------------------------------------|-----------|---------------------------|
| Early pulmonary tuberculosis..... | 51 cases. | Reacted 40 = 78 per cent. |
| Advanced pulmonary tuberculosis... | 21 " | " 14 = 67 " |
| Arrested pulmonary tuberculosis... | 7 " | " 5 = 71 " |
| Pulmonary tuberculosis with fever.. | 3 " | " 0 = 0 " |
| Glandular tuberculosis..... | 7 " | " 7 = 100 " |
| Bone tuberculosis..... | 19 " | " 16 = 84 " |
| Testicular tuberculosis..... | 3 " | " 2 = 67 " |
| Suspected pulmonary tuberculosis... | 28 " | " 14 = 50 " |
| Not tuberculosis | 32 " | " 1 = 37 " |

Emmerich ¹ has applied the test to 241 adults:

| | | |
|-----------------------------|-----------|---------------------------|
| Clinically tuberculous..... | 46 cases. | Reacted 24 = 52 per cent. |
| " tuberculosis suspected.. | 51 " | " 40 = 78 " |
| " not tuberculosis..... | 144 " | " 47 = 32.6 " |

Heinemann ² reports the following results:

| | | |
|-----------------------------------------------------|----------|-----------|
| Clinically pulmonary tuberculosis, first stage..... | 8 cases. | Reacted 7 |
| Second stage.... | 12 " | " 11 |
| Third stage..... | 4 " | " 1 |
| " tuberculosis suspected..... | 17 " | " 16 |
| " not tuberculosis..... | 25 " | " 8 |

The patients in this group had received the conjunctival test several months before the percutaneous, and Heinemann recognized that the general hypersensitiveness might have been stimulated by the primary application. To exclude this possibility he applied the test to another series of cases which had not previously received tuberculin:

| | | |
|-----------------------------------------------------|-----------|-----------|
| Clinically pulmonary tuberculosis, first stage..... | 10 cases. | Reacted 9 |
| Second stage... | 6 " | " 5 |
| Third stage..... | 4 " | " 0 |
| " tuberculosis suspected..... | 17 " | " 15 |
| " not tuberculosis..... | 71 " | " 12 |

¹ Emmerich: Ueber die klinische Bedeutung der kutanen und perkutanen Tuberkulinreaktion (nach v. Pirquet und nach Moro) beim Erwachsenen. München. med. Wehnschr., 1908, lv, 1066.

² Heinemann: Vergleichende Untersuchungen mit der Konjunktivalreaktion nach Wolff-Eisner, und der Salbenreaktion nach Moro. München. med. Wehnschr., 1908, lv, 556.

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The totals from the two tables give:

| | | | | |
|--------------------------------------|-----------|---------|----------|-----------|
| Pulmonary tuberculosis, first stage. | 18 cases. | Reacted | 16 = 90 | per cent. |
| Second stage. | 18 | " | 16 = 90 | " |
| Third stage.. | 8 | " | 1 = 12.5 | " |
| Tuberculosis suspected..... | 34 | " | 31 = 91 | " |
| Not tuberculosis..... | 96 | " | 20 = 21 | " |

Webb¹ reports observations upon 155 individuals given the Moro test: 69 of this number reacted. Of 85 apparently normal individuals, 19 reacted. Of 15 well-marked cases of tuberculosis, 8 reacted. Of 39 suspected tuberculosis, 31 reacted. Of 12 clinically early cases, 11 reacted. Of the 19 apparently normal individuals who reacted, 14 were found, by other methods of investigation, to be distinctly tuberculous. Of the 66 who failed to react, 2 were later found to be tuberculous.

The Value of the Percutaneous Tuberculin Test in Diagnosis.—A comparison of the foregoing reports of the results obtained with the percutaneous tuberculin test makes evident at once a striking variation in the percentage of reactions obtained by different observers. In most reports the number of individuals tested is so small that this factor alone allows a wide range of error. What was said in the discussion of the value of the conjunctival test about the evident sources of error in clinical classification is equally applicable here. However, allowing for these factors, the variation is still so great that other causes for the discrepancy must be sought. The strength of the ointment does not play a rôle, for all the tests were made with the percentage of tuberculin prescribed by Moro. The conclusion is forced upon us that differences in the method of applying the test must play a part. Aside from the strength of the ointment the following details must influence the result:

¹ Webb: Integumental tuberculin reaction with report of 155 Moro in-unction reactions. Jour. Am. Med. Assn., 1908, li, 1271.

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1. The length of time the ointment is rubbed into the skin and the thoroughness with which the rubbing is done.

2. The condition of the skin where the test is applied.

An individual may by practice come to exert fairly uniform pressure in performing the test and thus in this particular his own results will be comparable. It is, however, too much to expect a number of investigators to employ a uniform technique. Wolff-Eisner has demonstrated what widely different results variations in the method of application may give.¹ Patterson has observed that reactions are more frequent and more marked when the skin has been previously rubbed with alcohol. Moro himself admits that children under one year of age do not react well. Wetzell thinks the test of little value in the aged on account of loss, through senile atrophy, of the ability of the skin to absorb. Even normal differences in the thickness of the skin and the blood supply will influence the outcome of the test.

Aside from these pertinent technical objections it will be seen that the information obtained from the test is intermediate between that furnished by the cutaneous and the conjunctival tests. Not so many tuberculous cases react to the percutaneous as to the cutaneous test, and, therefore, the former excludes clinical tuberculosis with less certainty than the latter. On the other hand, many more doubtful cases react to the percutaneous than to the 1-per-cent. conjunctival test, which impairs its significance in indicating the presence of active tuberculosis. For these reasons we deem the percutaneous test of far less value in diagnosis than either the cutaneous or the conjunctival test. As with the cutaneous test, what value it has bears principally upon tuberculosis in children. Under ten years of age a marked reaction is confirmatory evidence of the presence of clinical tuberculosis; a negative reaction does not exclude it as

¹ Wolff-Eisner: Versuche mit verschiedenen Tuberkel-bazillenderivaten. Berl. klin. Wehnschr., 1908, lxx, 1400.

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surely as does the cutaneous test. Wolff-Eisner, Bandelier and Roepke and others say the percutaneous test is a valuable substitute for the cutaneous test when there is strong objection to any procedure savoring of vaccination. The cutaneous test is so simple and so easy to apply that we deem such an exigency more fanciful than real.

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Mendel¹ suggested that infiltration of the skin with tuberculin after the Schleich method of injection for anesthesia would be a delicate and satisfactory means of determining tuberculin hypersensitiveness. The suggestion has been developed and extensively used in man by Mantoux,² in animals by Römer.³ The test is performed by injecting from a sterile syringe the 1-20 of a c. c. of a dilute solution of tuberculin through a fine needle, the point of which has been inserted into the skin. After cleaning the skin of the forearm with alcohol it is drawn taut, with the left hand held under the arm, and the needle introduced, with the aperture directed toward the outer surface of the skin. If the point of the needle is in the skin a white elevation occurs immediately upon the introduction of the solution, if in the subcutaneous tissue no infiltration is apparent. Mantoux employs a 1 to 10,000 dilution of tuberculin, thus injecting 0.005 mg. of tuberculin. We have found it convenient to inject dilutions of increasing strength. As the tuberculin is absorbed, large amounts cannot be given without the risk of producing constitutional reactions. In per-

¹ Mendel: Die von Pirquetsche Hautreaktion und die intravenöse Tuberkulinbehandlung. *Med. Klin.*, 1908, iv, 402.

² Mantoux: Cited from *Münch. med. Woch.*, 1908, No. 40.

³ Römer: Zur Verwertung der intrakutanen Reaktion auf Tuberkulin. *Beitr. z. Klin. d. Tuberk.*, 1909, xiv, 1.

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forming the test we make four simultaneous injections. The first consists of 1-20 c. c. pure salt solution as a control; the second of 1-20 c. c. of a 1-to-1,000,000 dilution of old tuberculin, equals 0.00005 mg.; the third of 1-20 c. c. of a 1 to 100,000 dilution of old tuberculin, equals 0.0005 mg.; the fourth, of 1-20 c. c. of a 1 to 10,000 dilution of old tuberculin, equals 0.005 mg. If none of these areas react, we may perform a second test upon the opposite arm, injecting 1-20 c. c. of a 1 to 1,000 dilution of old tuberculin, equals 0.05 mg., and 1-20 c. c. of a 1 to 100 dilution of old tuberculin, equals 0.5 mg. In this way a more accurate estimate of the degree of hypersensitiveness is obtained than from a single injection. The test is very delicate and satisfactory results can be obtained only by exercising extreme precaution. Five new syringes must be selected and one marked for use with each dilution of tuberculin, and never be used for any other strength. In cleaning the syringes the wash water must not be ejected into the sterilizer. We have been able to obtain satisfactory results only by boiling the syringe used for making the control injection of sterile salt solution in a separate dish in which syringes used for tuberculin injections never come.

The reaction consists of infiltration and hyperemia about the site of injection analogous to the reaction to the cutaneous test. It appears in from six to eight hours, reaches its maximum in from twenty-four to forty-eight hours and usually disappears in from six to ten days. The injection of sterile salt solution into the skin is followed by a definite traumatic reaction, indistinguishable from a mild tuberculin reaction. This reaction is at its maximum after twenty-four hours and completely disappears in forty-eight hours. In order to use the salt solution as a control the tests must be read forty-eight hours after they are given.

The simplest method of recording the results is to meas-

THE INTRACUTANEOUS TUBERCULIN TEST

ure the width of the area of infiltration of each reacting point.

The only available statistics of the application of the intracutaneous test to man are in a report of Mantoux and Lemaire¹ upon the results of the test in 300 apparently healthy children. Among the children from a tuberculous environment in the first year of life 16 per cent. reacted; in the second and third, 51 per cent.; from the fourth to the sixth, 65 per cent.; from the seventh to the fourteenth, 84 per cent. Among children not so intimately exposed to the disease in the first year of life 11 per cent. reacted; in the second and third year, 12 per cent.; from the fourth to sixth year, 45 per cent.; from the seventh to the fifteenth year, 66 per cent. Although the number of cases is small, the figures indicate that the test is more delicate than the cutaneous test. Mantoux and Roux² performed the intracutaneous test and the cutaneous test simultaneously upon 52 children and found the former far more delicate than the latter.

In animals Römer has used the method with signal success. He finds it not only of value in diagnosis, but believes that the degree of reaction runs parallel with the severity of the infection. While the intracutaneous test is of the greatest value in the study of the prevalence of tuberculous infection, it is apparent that clinically it has but slight value in diagnosis. As a practical procedure it has no advantage over the simpler cutaneous test. However, as a means of estimating the degree of tuberculin hypersensitiveness, the test has no equal. Of what value such quantitative tests may be we shall later speak.

¹ Mantoux and Lemaire: *Intradermo réaction à la tuberculine chez 300 enfants non malades*. *Semaine méd.*, 1909, xxix, 371.

² Mantoux and Roux: *Cit. München. med. Wehnschr.*, 1908, lv, 2117.

THE SUBCUTANEOUS-LOCAL OR DEPOT TUBERCULIN TEST

Epstein¹ in 1891 was the first to describe the redness and swelling that occur about the point of the subcutaneous injection of tuberculin as a specific reaction. Escherich in 1892 gave it the name "stichreaktion." The specific character of the reaction was emphasized by v. Pirquet and Schick in their monograph published in 1903 and in the following year Schick² published the results of a study of the tuberculin experiences in the Graz Kinderklinik and further established the point. Klingmüller³ studied the local reaction histologically and pointed out its tuberculous structure. Spengler used the local reaction in an effort to differentiate human and bovine infection, and it was through his studies that Hamburger's attention was drawn to the subject. Hamburger⁴ has applied the test extensively and has developed it as a diagnostic procedure.

The subcutaneous-local reaction is usually employed supplementary to the cutaneous test. Being more delicate than the latter, it is always positive when the cutaneous test is positive. If the cutaneous test is negative Hamburger administers 0.1 c. c. of a 1 to 1,000 or a 1 to 10,000 dilution of original tuberculin, thus injecting either 1-10 or 1-100 of a mg.

The flexor surface of the forearm is usually selected as the position for applying the test, although other portions of the body may be used. The reaction is most striking

¹ Epstein, cit. Hamburger: Ueber den Wert der Stichreaktion nach Tuberkulininjektion. Wien. klin. Wchnschr., 1908, xxi, 381.

² Schick: Die diagnostische Tuberkulinreaktion im Kindesalter. Jahrb. f. Kinderh., 1905, lxi, 811.

³ Klingmüller: Beiträge zur Tuberkulose der Haut. Arch. f. Dermat. u. Syph., 1904, lxix, 167.

⁴ Hamburger: Ueber den Wert der Stichreaktion nach Tuberkulininjektion. Wien. klin. Wchnschr., 1908, xxi, 381.

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where the skin is thin. For this reason Tedeschi has suggested using the ear.¹ The skin is cleaned with alcohol and the needle of the syringe then carefully introduced into the subcutaneous tissue immediately under the skin. The volume of the injection should not exceed 0.1 c. c. The injection should be given toward the body and the needle introduced with the outlet directed toward the skin so that the tuberculin will be deposited as near as possible to the surface. The same precaution is necessary in regard to the syringe as in performing the intracutaneous test. If the reaction is positive, redness and infiltration begin about the area of injection in from four to eight hours, and reach their maximum in twenty-four hours. It is very rare for a test negative at the end of twenty-four hours to become frankly positive later. The area of redness and infiltration varies greatly in size and if the reaction be severe the adjacent lymph glands may become swollen. The reaction may usually be divided into two distinct features, a small area of redness at the point where the needle has pierced the skin, and the larger area of subcutaneous infiltration. The distance between the two depends upon the distance the needle is introduced. When the reaction is severe the two coalesce. Schlossman has suggested calling the area of skin redness the "stichreaktion," the subcutaneous infiltration the "depot reaktion." However, the term "stichreaktion" has from long usage become identified with the whole local reaction and the proposed division is confusing and has no practical advantage. The area of infiltration is usually tender. Mild constitutional symptoms and temperature elevation may accompany the reaction. The infiltration usually disappears in from five to seven days but severe reactions may persist for weeks.

Hamburger has found that when the cutaneous test is

¹ Tedeschi: Ueber Tuberkulinreaktionen speciell über eine Auriculoreaktion. Arch. f. Kinderh., 1909, xlix, 189.

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positive there is constantly a reaction to 0.001 mg. or 1-10 c. c. of a 1 to 100,000 dilution injected subcutaneously. To avoid making a number of preliminary tests he tries first the cutaneous reactivity. If this be negative a subcutaneous injection of 0.01 or 0.1 mg. in 1-10 c. c. volume will frequently give a decided reaction. He occasionally gives 1 mg. but finds that as a rule it is unnecessary to go beyond 0.1 mg., for an individual negative to this amount but rarely shows a reaction to higher doses. The preliminary cutaneous test diminishes the chances of a constitutional reaction. In comparing the cutaneous and the subcutaneous-local reactions Hamburger comes to these conclusions:

1. Every case with a positive cutaneous reaction is positive to subcutaneous injections of 0.001 mg.

2. Many cases negative or doubtful to the cutaneous test react to 0.1 or 0.01 mg. given subcutaneously.

3. All of these cases when retested later give a positive cutaneous test (stimulation of hypersensitiveness).

4. Cases negative to 0.1 mg. subcutaneously but rarely subsequently give a cutaneous reaction or a subcutaneous reaction to large doses of tuberculin.

5. Cases negative to the cutaneous test and positive to the subcutaneous have nearly all inactive latent lesions. However, a small number of individuals with active manifest lesions who fail to react to the cutaneous test do react to the subcutaneous.

6. Individuals reacting to 0.001 mg. (1 to 100,000) subcutaneously give a cutaneous reaction; individuals reacting to 0.0001 mg. (1 to 1,000,000) or to 0.000,001 mg. (1 to 100,000,000) give a marked cutaneous reaction; individuals reacting only to 0.01 mg. (1 to 10,000) or to 0.1 mg. (1 to 1,000) do not give a cutaneous reaction.

Hamburger reports the results of the test applied to 200 children:

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| Age. | Cutaneous and Subcutaneous Tests, Both Negative. | Cutaneous and Subcutaneous Tests, Both Positive. | Cutaneous Negative, Subcutaneous Positive. | Total. |
|---------------------|-----------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------|-----------|
| 1 year..... | 26 | 2 | 1 | 29 |
| 2 years..... | 16 | 4 | 2 | 22 |
| 3 and 4 years..... | 24 | 7 | 2 | 33 |
| 5 and 6 years..... | 17 | 8 | 5 | 30 |
| 7 to 10 years..... | 14 | 21 | 18 | 53 |
| 11 to 14 years..... | 5 | 16 | 12 | 33 |
| | <hr/> 102 | <hr/> 58 | <hr/> 40 | <hr/> 200 |

With increasing years the number of latent infections increase, and, as one would predict, the two tests practically coincide in the first two years of life while the subcutaneous, the more sensitive test, shows a much larger number of reactions in older children.

Similar results are obtained by Hamburger and Monti¹ on a much larger number of children. The material comprises children in whom there is clinically no suspicion of tuberculosis, convalescent from acute infectious diseases.

| | |
|---------------------------------|----------------------------------|
| 46 children in second year..... | 9 per cent. react subcutaneously |
| 56 " " third " | 20 " " " |
| 75 " " fourth " | 32 " " " |
| 50 " " fifth " | 52 " " " |
| 63 " " sixth " | 51 " " " |
| 46 " " seventh " | 61 " " " |
| 30 " " eighth " | 73 " " " |
| 35 " " ninth " | 71 " " " |
| 26 " " tenth " | 85 " " " |
| 29 " " eleventh " | 93 " " " |
| 19 " " twelfth " | 95 " " " |
| 17 " " thirteenth " | 94 " " " |
| 17 " " fourteenth " | 94 " " " |

The authors arrived at these figures by applying first the cutaneous test; if this is negative two days later a sub-

¹ Hamburger and Monti: Die Tuberkulosehäufigkeit in Kindesalter. München. med. Wehnschr., 1909, lvi, 449.

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cutaneous injection of 0.01 mg. or 0.1 mg. was given in the forearm. In a few instances negative to this test a second injection of 1 mg. was administered.

To show the relation of the subcutaneous-local reaction to the cutaneous reaction and the correspondence of each with autopsy findings, Hamburger and Monti prepare the following table:

| SECTIONS GHON'S MATERIAL | | TUBERCULIN REACTIONS | | | |
|------------------------------------|-----------------------|----------------------|----------------------|---------------------|-----------------------------|
| Lethal and Non-lethal Tuberculosis | Minimal or Non-lethal | Pirquet Cutaneous | Ganghofner Cutaneous | Hamburger and Monti | |
| | | | | Cutaneous | Cutaneous and Sub-cutaneous |
| II. 2nd year..... | 40 | 17 | 2 | 12 | 9 |
| III. 3rd and 4th year..... | 60 | 30 | 13 | 27 | 23 |
| IV. 5th and 6th years..... | 56 | 34 | 17 | 47 | 36 |
| V. 7th to 10th year..... | 63 | 35 | 35 | 51 | 47 |
| VI. 11th to 14th year..... | 70 | 53 | 55 | 70 | 51 |

Nothmann¹ reports observations upon the tuberculin reactivity of 244 children. They were all given the cutaneous test; those negative were given a second cutaneous test; those still negative were then given the subcutaneous-local test:

| | |
|------------------------------------------|--------------------------|
| Of 15 children from 3 to 5 years of age, | 7 reacted = 47 per cent. |
| " 25 " " 6 " 7 " " | 14 " = 56 " |
| " 41 " " 8 " 9 " " | 29 " = 70.7 " |
| " 54 " " 10 " 11 " " | 44 " = 81.5 " |
| " 97 " " 12 " 14 " " | 82 " = 84.5 " |
| " 12 " " 15 " 17 " " | 12 " = 100 " |

To the first cutaneous test, 47.1 per cent. of the children reacted, to the first plus the second 65.7 per cent., to the first and the second plus the subcutaneous-local test 77 per cent. reacted.

¹ Nothmann: Ueber die Häufigkeit der Tuberkulose im Kindesalter. Berl. klin. Wehnschr., 1910, xlvii, 381.

OTHER METHODS OF PERFORMING TUBERCULIN TEST

The subcutaneous-local reaction is, then, a more sensitive indication of tuberculous infection than the cutaneous test and therefore excludes more completely than the latter does the presence of tuberculous disease. Hamburger¹ has shown that an occasional instance of active tuberculosis missed by the cutaneous test will be revealed by a subcutaneous local reaction. However, in adult life and even in late childhood the test has absolutely no diagnostic value, since only an occasional individual will escape its searching scrutiny. What little diagnostic value it has is restricted to the first two years of life and even at that age it has no marked value above the cutaneous test. What we chiefly owe to the subcutaneous-local test is the astonishing revelation of the extent to which man is tuberculosis-infected and at what an early age the infection occurs.

OTHER METHODS OF PERFORMING THE TUBERCULIN TEST

When an individual is hypersensitive to tuberculin all of the cells and tissues of the body acquire the property of reacting to tuberculin. Not only the conjunctival mucous membrane displays the reactivity but all other mucous membranes become inflamed following tuberculin application. Methods other than the conjunctival test have been suggested as diagnostic procedures. We mention them not because they have practical importance but on account of their general interest. Why they do not lend themselves to general use will be at once apparent and indeed it is difficult to believe that some of them are seriously proposed. It is occasionally observed that, associated with an active conjunctival reaction there are redness of and secretion from the nasal mucous membrane on the same side. The

¹ Hamburger: Ueber die Stichreaktion bei der Diagnose kindlicher Tuberculose. München. med. Wehnschr., 1909, lvi, 22.

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reaction follows the drainage of tuberculin through the tear duct. Lafite-Dupont and Molinier¹ have suggested utilizing the nasal mucous membrane as the point to be tested. They apply for ten minutes a tampon moistened with 1 per cent. tuberculin. Redness and secretion occur in from eighteen to twenty-four hours.

Oppenheim in 1907 suggested using the mucous membrane of the male urethra. Pagano² has studied the question in detail and advises its use. During the reaction there is a urethral discharge. Plehn³ has described a pharyngeal tuberculin test. Schnürer⁴ has utilized the vaginal mucous membrane in cows. To our knowledge his method has not been applied to human beings. Jacob⁵ in an elaborate study has shown that reactions may follow the infusion of tuberculin into the lungs. Kapralik and Schrötter⁶ have made similar observations on the results of tuberculin inhalations by means of a specially constructed spray.

These two methods were suggested as advantageous means of therapeutic application. Without considering other disadvantages the uncertain dosage alone renders them undesirable for practice.

The stomach has also been advocated as a route for tuberculin administration. By this means not a local but a

¹ Lafite-Dupont and Molinier: Réaction diagnostique de la tuberculine sur la muqueuse nasale. *Presse méd.*, 1909, xvii, 180.

² Pagano: L'uretroreazione alla tuberculina. *Rev. critica di clinica med.*, 1908, ix, 597.

³ Plehn: Die Ophthalmoreaktion auf Tuberkulin als diagnostisches Hilfsmittel. *Deutsch. med. Wehnschr.*, 1908, xxxiv, 315.

⁴ Schnürer, cited v. Pirquet: Die lokalen Tuberkulinreaktion. Kraus and Levaditi: *Handbuch der Technik und Methodik der Immunitätsforschung*. Erster Ergänzungsband, Jena, 1911, p. 191.

⁵ Jacob: Ueber die Bedeutung der Lungeninfusionen für die Diagnose und Therapie der Lungentuberkulose. *Deutsch. med. Wehnschr.*, 1904, xxx, 945.

⁶ Kapralik and Schrötter: Erfahrungen über die Wirkung der Einführung von Tuberkulin im Wege des Respirations-Apparates. *Wien. klin. Wehnschr.*, 1904, xvii, 583.

SECONDARY OR RECURRENT REACTIONS

general reaction is sought. It would seem that reactions may be liberated but the evidence is by no means conclusive. Freymuth has used keratin-covered pills of tuberculin administered by mouth in diagnosis. The overwhelming evidence of numerous observers (Huhs,¹ Loewenstein, Köhler, Bandelier and Roepke) proves the method to be without value.

Calmette and Breton² claim that an enema of 0.019 mg. of tuberculin will produce fever in the tuberculous. Pfeiffer³ could not confirm their results.

SECONDARY OR RECURRENT REACTIONS

It has long been known that during a general reaction to the subcutaneous administration of tuberculin points where tuberculin had previously been injected display a tendency to show an inflammatory reaction. This tendency is particularly well marked in the conjunctiva and skin when the conjunctival and cutaneous tests have preceded the subcutaneous injections. These areas may flare up even when the tests were originally negative. A study of sixty-eight patients who received the cutaneous and conjunctival test and were subsequently given the subcutaneous tuberculin test revealed these relations:

1. Conjunctival and cutaneous secondary reactions may follow subcutaneous injections of tuberculin whether the original tests were negative or positive.
2. Secondary reactions are more common when the original test was positive.
3. When both the 1-per-cent. and the 5-per-cent. con-

¹ Huhs: *Therapeutische Versuche mit stomachaler und inhalatorischer Darreichung von Alttuberkulin*. Beitr. z. Klin. d. Tuberk., 1907, vii, 1.

² Calmette and Breton, cited v. Pirquet: *Die lokalen Tuberkulinreaktion*. Kraus and Levaditi: *Handbuch der Technik und Methodik der Immunitätsforschung*. I Ergänzungsband. Jena, 1911, p. 191.

³ Pfeiffer: Cit. v. Pirquet, *ibid*.

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conjunctival tests have been given the conjunctiva having received 5 per cent. shows a secondary reaction to smaller subcutaneous doses than the conjunctiva having received 1 per cent.

4. The conjunctival and cutaneous test areas usually both flare up, although occasionally one may show a secondary reaction while the other does not.

5. As a rule secondary reactions occur only when the subcutaneous dose is large enough to liberate a general reaction. However, they do at times appear when no constitutional reaction occurs. In such instances the subcutaneous injection has always produced a local reaction.

6. There may be a well-marked constitutional reaction without secondary reactions even though the original cutaneous and conjunctival tests were negative.

7. The size of the subcutaneous dose and the intensity of the general reaction bear no relation to the occurrence of secondary reactions.

8. There may be no secondary reaction to a subcutaneous dose liberating a general reaction, even though a secondary reaction may have occurred after a previous smaller dose unassociated with a general reaction. Generally, however, each succeeding subcutaneous dose is followed by an increasingly severe flare-up.

9. The cutaneous secondary reaction is usually accompanied by a wider area of redness than was the original reaction but the infiltration is less marked.

10. Secondary reactions never occur in non-infected individuals. Like all tuberculin reactions, they are strictly specific and indicate always the presence of tuberculous infection.

11. The shortest lapse of time between the original test and the flare-up was eleven days, the longest five months.

The occurrence of secondary reactions may prove embarrassing for both diagnostic and therapeutic injections

RELATION OF VARIOUS TUBERCULIN TESTS

of tuberculin. In diagnosis they may be so severe as to make further injections inadvisable and thus prevent the detection of a focal reaction. Their constant recurrence during treatment, it is said, may force the abandonment of further tuberculin injections. This necessity has not befallen us during tuberculin treatment, as we have rarely observed recurrent reactions to the small, slowly increasing doses that we employ.

It has been reported that a conjunctival reaction may repeatedly flare up when exercise is subsequently indulged in. Presumably such recurrences are caused by the auto-inoculation the exercise induces. Fortunately such an occurrence must be very rare, for we have ourselves never personally observed an instance.

RELATION OF THE VARIOUS TUBERCULIN TESTS TO ONE ANOTHER

One would presume that the reactivity to a given tuberculin test would always wear a constant relation to the sensitiveness for the other tests. We have pointed out that the cutaneous test is a far more delicate index of tuberculin hypersensitiveness than the conjunctival test. It is reasonable to expect that by using a weaker dilution of tuberculin for the cutaneous test we might come to a point where a skin reaction to a given dose would indicate the degree of hypersensitiveness necessary to liberate a conjunctival reaction. Likewise the degree of sensitiveness to the cutaneous or intracutaneous test might enable us to predict the dose of tuberculin which will liberate a general reaction. Such relations have been diligently sought for and, while a few investigators believe they exist, most have failed in their efforts to demonstrate them. We have already spoken of the different susceptibility to the cutaneous test of the different areas of skin. This difference may depend upon

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variation in the actual tuberculin sensitiveness of the cells or in mechanical factors influencing absorption. That similar local differences exist between different methods of applying tuberculin must be evident and unfortunately the degree of variation is largely individual, since we are unable to accurately predict the degree in a given instance. While the cutaneous test is in general far more delicate than the conjunctival, we not infrequently obtain a positive conjunctival reaction when the cutaneous test is negative. Without having figures to support the view, we have gotten the impression that in advancing disease the skin loses its ability to react earlier than the conjunctiva. We frequently see in advanced cases a negative cutaneous and mildly positive conjunctival reaction. Occasionally a conjunctival test is positive and the subcutaneous test negative.

In 990 cases that we have analyzed, where the cutaneous and conjunctival tests were given simultaneously, 13 who gave a conjunctival reaction failed to react cutaneously. Of the 811 cases that reacted cutaneously 297 gave a conjunctival reaction. The details are given in the following table:

| CONJUNCTIVAL REACTIONS TO FIRST INSTILLATION OF 1 PER CENT. | | | | | | | | | |
|-------------------------------------------------------------|-------|-----------------------|---------|-----|---------|-----|---------|-----|---------|
| REACTIONS | CASES | SKIN REACTIONS (PURE) | | | | | | | |
| | | + | | ++ | | +++ | | | |
| | | No. | Per Ct. | No. | Per Ct. | No. | Per Ct. | No. | Per Ct. |
| -..... | 680 | 166 | 24 | 418 | 62 | 80 | 12 | 16 | 2 |
| +..... | 153 | 8 | 5 | 118 | 77 | 24 | 15 | 3 | 2 |
| ++..... | 97 | 3 | 3 | 60 | 64 | 25 | 26 | 9 | 9 |
| +++..... | 60 | 2 | 3 | 29 | 48 | 18 | 30 | 11 | 18 |

Forty-eight of our cases who had received the conjunctival and cutaneous tests were subsequently given tuberculin subcutaneously:

Two cases were entirely negative to the subcutaneous

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test; none of these gave a conjunctival reaction; none gave a cutaneous reaction.

Thirteen cases gave a local reaction to the subcutaneous injections, but no general or febrile reaction; one gave a positive conjunctival test; 10 gave a positive cutaneous test.

Thirty-three cases gave a constitutional reaction to the subcutaneous test; 8 gave a positive conjunctival test; 30 gave a positive cutaneous test.

We have attempted to parallel the cutaneous test with the conjunctival test by using various strengths of tuberculin upon the skin. As the accompanying table shows, the attempt was unsuccessful.

| CONJUNCTIVAL REACTIONS TO FIRST INSTILLATION OF 1 PER CENT. | CUTANEOUS REACTIONS | | | | | |
|-------------------------------------------------------------------|---------------------|-----------|-------------|-----------|--------------|-----------|
| | 1 Per Cent. | | 5 Per Cent. | | 20 Per Cent. | |
| | Number | Per Cent. | Number | Per Cent. | Number | Per Cent. |
| Negative.....340 | 69 | 20 | 187 | 54 | 241 | 81 |
| + Reaction.....80 | 43 | 53 | 62 | 76 | 71 | 89 |
| ++ ".....63 | 31 | 49 | 54 | 85 | 58 | 92 |
| +++ ".....35 | 25 | 71 | 32 | 91 | 34 | 97 |

Hamill, Carpenter and Cope compare the conjunctival, the cutaneous, the percutaneous and the subcutaneous tests. In giving the subcutaneous test the maximum dose was 1 mg. and in most instances it was not over 0.5 mg. Many cases received a single injection of 0.1 mg. The conjunctival test was performed with a 0.5-per-cent. precipitated tuberculin. The tests were made upon children.

All four tests were made in 83 instances. In this number there was complete agreement between the tests; that is, all were negative or all positive seventy-seven times. Once the conjunctival and subcutaneous tests were positive, the cutaneous and percutaneous tests negative. One patient negative to the subcutaneous test was positive to the other

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three. One negative to the conjunctival test was positive to the other three. The cutaneous test was negative and the others positive in three instances. The conjunctival test was positive and the other three negative in one instance.

Such almost uniform agreement is most unusual. In children, of course, one would anticipate greater uniformity than in adults.

Mainini¹ performed the cutaneous and the conjunctival test upon 100 individuals. The conjunctival test was performed with a 5-per-cent. solution of old tuberculin. Forty-five reacted to the conjunctival test, ninety-two to the cutaneous.

Stadelmann and Wolff-Eisner² obtained 149 cutaneous and 81 conjunctival reactions in 276 individuals. They use 1-per-cent. old tuberculin for the conjunctival test.

Engelbach and Shankland in 63 normal individuals observed 33 cutaneous and 15 conjunctival reactions. Twenty-one cases gave a positive cutaneous and a negative conjunctival test. Three gave a positive conjunctival and a negative cutaneous test.

Patterson in 171 instances found the cutaneous reaction positive in 122, the percutaneous in 94.

Emmerich in 121 cases obtained 92 reactions to the cutaneous test and 59 to the percutaneous.

Heinemann in 66 individuals found 43 reacted to the percutaneous and 34 to the conjunctival test.

Gordon³ administered the cutaneous and then the subcutaneous test to 84 patients. Of 41 cases with negative skin reactions 40 were negative to subcutaneous injections of 5 and, in some instances, of 10 mg. Of 40 cases positive

¹ Mainini: Haut- und Ophthalmoreaktion auf Tuberkulin. München. med. Wehnschr., 1907, liv, 2583.

² Stadelmann and Wolff-Eisner: Ueber kutane und conjunctivale Tuberkulinreaktion. Deutsch. med. Wehnschr., 1908, xxxiv, 180.

³ Gordon: The relation of the cutaneous to the subcutaneous tuberculin test. Nat. Assn. for the Study and Prevention of Tuberc., 1910, vi, 217.

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to the cutaneous test 36 reacted to subcutaneous injections of from 1 to 3 mg.

White and Van Norman¹ by special methods of performing the cutaneous test have claimed to be able to predict accurately the dose of tuberculin which, injected subcutaneously, will liberate a general reaction. A discussion of their results is reserved for the section on Quantitative Tuberculin Tests.

If we compare with these figures obtained by performing different tests upon the same person those already given for the relative frequency of the individual tests, we have a foundation for these conclusions:

1. The intracutaneous and the subcutaneous-local tests are the most delicate we possess. They reveal practically the full percentage of tuberculosis-infected individuals.

2. In the order of their sensitiveness the tests arrange themselves as follows:

Intracutaneous Test.

Subcutaneous-local Test.

Cutaneous Test.

Subcutaneous Test.

Percutaneous Test.

Conjunctival Test.

3. There is a definite but not a constant relation between the various tests. An individual reacting to the conjunctival test will, as a rule, give all the others, but not always. The cutaneous or the subcutaneous tests may be negative when the conjunctival is positive. The subcutaneous positive when the cutaneous is negative, etc. Some of these unusual variations may no doubt depend upon faulty technique in performing the tests, but all can certainly not be thus explained. Local changes in sensitive-

¹ White and Van Norman: An individual quantitative basis for dosage in tuberculin treatment. *Ibid.*, 224.

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ness and variation in the facility of absorption are probable factors but the exact conditions are not understood.

4. We have been unsuccessful in an attempt to make the cutaneous test with different strengths of tuberculin equivalent to the conjunctival test.

THE DIFFERENTIAL CUTANEOUS REACTION

Detre¹ has described a so-called differential cutaneous reaction. This, in brief, consists in performing von Pirquet's test by the simultaneous application, in series, of human old tuberculin and of human and bovine bouillon filtrates. Then, measuring the resulting reactions in millimeters, he believes himself able to draw reliable conclusions as to whether the patient has been infected with the bacillus of the human or bovine type, and as to whether the disease at the time of the test is active or latent. His theoretical premises are that a person infected with the human type of organism will react more strongly to the human filtrate than to the bovine, and *vice versa*. He also supposes that a patient exhibiting active signs of disease will yield a papule to the filtrate larger than or as large as the papule produced by the old tuberculin, and that the inverse relation will be found in patients with a non-progressive lesion. He thus differentiates acute and chronic human and bovine types and mixed types. That the human type may give a predominant and not necessarily an exclusive human reaction he attributes to some common properties of the bovine and human organisms. The predominant reaction to the filtrate in active cases he explains by the presence in the filtrates of a thermolabile toxin which is destroyed in the process of concentrating by heat the old tuberculin. To this toxin the body, according to him, is

¹ Detre: Differentielle Tuberkulinreaktionen. Wien. klin. Wchnschr., 1908, xxi, 173.

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quickly sensitized during the process of a lesion, and with its arrest "autoimmunization" to this toxin occurs. Autoimmunization to the protein bodies of the old tuberculin he considers a rarer and more difficult occurrence.

Whatever is to be said as to the theoretical basis of Detre's work, we can not agree to the results obtained by him. Not only does our work strongly contradict his results but we find, both in the nature of the phenomena and in his technique, serious objections to his procedure, and still more serious objections to his drawing conclusions therefrom. The whole structure of Detre's data and conclusions rests on the measurement of the diameter of the cutaneous reaction consequent on an abrasion by the boring method of von Pirquet. In looking over his tables it can be seen that some of his cases are assigned their respective positions in the classification on the basis of a difference of only one or several millimeters in the diameter of the papule. Our own experience with the skin test makes us feel skeptical as to conclusions built on such minute differences as these. And the work of Schütz and Vidéky¹ strongly confirms us in our attitude. These authors, by careful measurements, by the application in series of tuberculins of varying strengths, by the application of the same solution in various parts of the body, have shown that the greatest variation in the size of the papules may result from no determinate factor. Using the same solution for several abrasions, they find large variation in the diameter of the papule—fully as large as the differences on which Detre stakes so much. In studying dilutions of various strengths, they find the same disappointing irregularity. In brief, they conclude that the difficulties in technique combined with

¹ Schütz and Vidéky: Ueber den Zusammenhang der exsudativen (phlyktänulären) Augenerkrankungen und der Tuberkulose nebst Erfahrungen über den Wert der kutanen und subkutanen Tuberkulin-diagnostik. Wien. klin. Wehnschr., 1908, xxi, 1285.

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the varied reactive and absorptive power of the different areas of skin make it impossible to use the size of the papule as a basis of anything respectable in reference. Von Pirquet,¹ too, states that variations below 50 per cent. in the diameter of a papule may be due to unavoidable differences in technique. Moreover, Schütz and Vidéky point out the great importance of remembering the various periods at which papules (even when due to the same tuberculin) reach their maximum. Assuming even that Detre's technique is all that we can not expect it to be, he has entirely neglected the time relations in deciding which is the predominant papule. What is the predominant papule to-day may not preserve that distinction to-morrow.

We report, however, 150 cases in which tests were given somewhat according to his procedure. On the forearm four solutions were used in the following order: human O. T., bovine O. T., human bouillon filtrate, bovine bouillon filtrate, all undiluted. Borrowing Detre's nomenclature, the following classification is convenient:

Group 1. The H. O. T. papule positive, the others slight or negative (old human lesion).

Group 2. The H. O. T. more marked than the H. B. F. (old human lesion).

Group 3. The H. B. F. more marked than the H. O. T. (active human lesion).

Group 4. The B. O. T. and the B. B. F. positive, but the B. O. T. the more so. The others slight or negative (old bovine lesion).

Group 5. Same as 4, but the B. B. F. more marked than the B. O. T. (active bovine lesion).

Group 6. The H. O. T. and the B. O. T. equal and more intense than the H. B. F. and the B. B. F. (old mixed lesion).

¹ von Pirquet: Verlauf der tuberkulösen Allergie bei einem Falle von Masern und Miliar-tuberkulose. Wien. klin. Wchnschr., 1908, xxi, 861.

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Group 7. The H. B. F. and the B. B. F. equal, but more intense than the H. O. T. and the B. O. T. (active mixed lesion)

Group 8. All the papules approximately alike.

RESULTS IN 150 CASES WITH DETRE'S DIFFERENTIAL CUTANEOUS TEST.

| | NON-TUBERCULOUS CASES | DOUBTFUL CASES | PROBABLE CASES | INCIPIENT CASES | | MOD. ADVANCED CASES | | FAR ADVANCED CASES | | TOTAL |
|------------|-----------------------|----------------|----------------|-----------------|-----------|---------------------|-----------|--------------------|-----------|-------|
| | | | | Active | Quiescent | Active | Quiescent | Active | Quiescent | |
| Group 1... | | 34 | 6 | 3 | 1 | 10 | 3 | 5 | ... | 62 |
| Group 2... | | 5 | 1 | 1 | ... | 2 | ... | 2 | ... | 11 |
| Group 3... | | 4 | ... | ... | ... | ... | ... | 5 | ... | 9 |
| Group 4... | | 1 | ... | ... | ... | ... | ... | ... | ... | 1 |
| Group 5... | | ... | ... | ... | ... | ... | ... | ... | ... | 0 |
| Group 6... | | 23 | 1 | 1 | ... | 4 | ... | 4 | 1 | 34 |
| Group 7... | | 3 | ... | ... | ... | 1 | ... | 1 | ... | 5 |
| Group 8... | | 22 | 1 | ... | ... | 4 | 1 | ... | ... | 28 |
| Total... | | 92 | 9 | 5 | 1 | 21 | 4 | 17 | 1 | 150 |

The above table shows the distribution of 150 cases in these 8 groups.

Groups 1, 2 and 3 would comprise, according to Detre, the human infection, equaling 54 per cent. of our cases.

Groups 4 and 5, comprising the bovine infection, contain together only one case, that is, 0.6 per cent. of our cases.

Groups 6, 7 and 8 embrace the mixed infection, 46 per cent. of our cases.

Detre's figures for his pulmonary cases are:

72 per cent. as compared with our 54 per cent. human.

19 per cent. as compared with our 46 per cent. mixed.

9 per cent. as compared with our 0.6 per cent. bovine.

Our results, as contrasted with his, point to the rarity with which the bovine papule predominates and to the frequency with which the bovine and the human papules are approximately alike.

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Groups 3, 5 and 7 comprise all the active cases, according to Detre's conception—active human, active bovine, and active mixed.

Together these groups hold 9 per cent. of our cases. Group 5, active bovine, has not a single case. The active human group has 9 cases; the active mixed groups, 5 cases. Detre, in 57 cases, has 45 per cent. in the active group. Analyzed further, of our 47 advanced cases 16 per cent. (7) are in the active group. Of our 107 early cases (embracing doubtful, probable and incipient cases) 6.5 per cent. (7) are in the active group. That is, the group of cases in which he would expect to find the largest number of active reactions yields a smaller number than the advanced cases. Detre finds that of his cases with a lesion more than two years old 23 per cent. are in the active group; of cases with lesions less than two years old 82 per cent. are in the active group. The number of his cases is scarcely one-third of those in the above table. It will be noted that the great bulk of our 150 cases, 124, in fact, fall into groups 1, 6 and 8—groups in which the old tuberculin has produced a papule larger or as large as the filtrates. It is also seen that the human O. T. tends to produce the larger papule.

These findings are in harmony with the results obtained in 150 of our cases other than the above, in which the human and the bovine old tuberculin were alone compared. The observation of these 150 cases was made before Detre's investigation came under our notice. It was undertaken in the hope of eliciting some therapeutic hints as regards the treatment of our patients who were not doing well on subcutaneous injections of human O. T. In only one of these 150 cases was the bovine reaction stronger than the human. In only 23 cases was the bovine reaction materially less than the human; in other words, the human and bovine old tuberculin tend to produce about the same-sized

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papule. In all our readings we attempted no unjustifiable finesse or even measurements by rule. We decided predominance of a papule by its manifest superiority over the rest. Lesser differences in either direction were ignored, for reasons above stated.

Our results indicate that if Detre's method is reliable, pure bovine infection is rare with us, while mixed infection is surprisingly frequent and pure human infection surprisingly low. As regards activity, our results would indicate that the activity fails to exist where it ought to be. But we have little confidence in the method. All that the work seems to show is that the filtrate produces weaker reactions than the O. T.—a result opposed to Detre's.

In order to have made our tables strictly comparable to Detre's in regard to the question of activity and chronicity we should have used 20 per cent. O. T. instead of undiluted O. T. We have previously found, however, that the 20 per cent. O. T. yields practically the same papule as concentrated O. T. We must bear in mind also the work of Schütz and Vidéky. But, even assuming that 20 per cent. solution gives only a proportionate papule, we should expect, if Detre's statement as to the frequent predominance of the filtrate is true, that more than 9 per cent. of our total cases should show an active reaction.

There are not enough data at the present time to permit an estimate of the general opinion of workers with the differential cutaneous reaction. Hamill, Carpenter and Cope¹ have published but 24 cases. The strongest support to Detre's results is from Heim and John.² Von Gebhardt³

¹ Hamill, Carpenter and Cope. A comparison of the von Pirquet, Calmette and Moro tuberculin tests and their diagnostic value. *Arch. Int. Med.*, 1908, ii, 405.

² Heim and John: Allergie und Tuberkulinfiltratproben nach v. Pirquet-Detre Fälle. *Wien. med. Wehnschr.*, 1908, xxi, 253.

³ von Gebhardt: Über die v. Pirquet-Detresche Kutanreaktion. *Ztschr. f. Tuberk.*, 1909, xiii, 345.

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finds that he can confirm Detre's observations of the tendency of the filtrate papule to be as distinct as and even more distinct than the old tuberculin papule. He finds the latter nearly always predominant; in fact, according to him, the remaining papules show little tendency to appear at all, unless the O. T. papule is quite strong. Kentzler¹ finds the H. O. T. papules by far the most marked. Schütz and Vidéky, as has been stated, think the whole scheme illusory.

THE VALUE OF TUBERCULIN TESTS IN PROGNOSIS

The value of tuberculin in prognosis has been emphasized chiefly by Wolff-Eisner.² In his original publication with Stadelmann he found that, whereas a large proportion of early cases of pulmonary tuberculosis react to the conjunctival test, relatively few advanced cases show a reaction. Subsequent experience has confirmed his confidence in these results. From a consideration of them and of a number of individual examples of their applicability he draws these conclusions:

1. A positive conjunctival reaction indicates active tuberculosis. Its occurrence, therefore, cannot be looked upon as prognostically favorable, but where the presence of tuberculosis has been established an active reaction indicates, other things being equal, a better prognosis than does a mild or absent reaction. The same significance is attached to the presence or absence of the normal cutaneous reaction.

2. In cases of conclusively established clinical tuberculosis a bad prognosis attaches to a negative conjunctival

¹ Kentzler: Ueber differenzierende Kutan-Tuberkulinreaktionen bei Erwachsenen. Wien. klin. Wchnschr., 1908, xxi, 14.

² Stadelmann and Wolff-Eisner: Ueber kutane und conjunctivale Tuberkulinreaktion. Deutsch. med. Wchnschr., 1908, xxxiv, 180; Wolff-Eisner: Frühdiagnose und Tuberkuloseimmunität. Würzburg, 1909, 326.

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test. A negative or premature cutaneous reaction has the same significance and it has this significance even though the conjunctival test be positive. A positive conjunctival test is, therefore, not always a favorable indication.

3. The (prolonged) cutaneous reaction occurs in clinically healthy individuals, those with healed lesions and those with very chronic, benign forms of the disease. It is always of favorable prognostic import.

Wolff-Eisner originally contended that the intensity of the reaction had prognostic significance; the more severe the reaction the more favorable the outlook. In his latest publication¹ he lays less emphasis upon this view. He complains that a number of investigators are unable to grasp how a test which is supposed to detect only active tuberculous lesions can at the same time indicate a favorable prognosis. We must allow that this objection is unimportant and that the paradoxical nature of the contention is not its refutation. As things go, it is by no means reassuring of future well-being to harbor an active tuberculous lesion, but if the misfortune exists there may well be clinical indications pointing to an ominous or more favorable outcome.

One must consider Wolff-Eisner's view from two standpoints: first, as regards the fact upon which the contention is based, and, second, as regards the conclusions deduced from the facts.

Our own experience does not agree with Wolff-Eisner's. In a large number of cases we have found that the moderately advanced cases of pulmonary tuberculosis give a larger per cent. of reactions than either the early or the far advanced cases. Our tables show this.

¹ Wolff-Eisner: *Frühdiagnose und Tuberkulose-Immunität*. 2nd edition. Würzburg, 1909, 229.

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ILLUSTRATING THE NUMBER PER HUNDRED OF REACTIONS TO THE
CUTANEOUS AND CONJUNCTIVAL TESTS IN 530 PATIENTS

| Strength of Tuberculin. | PER CENT. OF SKIN REACTIONS | | | | | | | | | | | | PER CENT. OF CONJUNCTIVAL REACTIONS | | | | | |
|-------------------------------------------|-----------------------------|----|----|-----|-------------|----|----|-----|--------------|----|----|-----|-------------------------------------|----|----|-----|-----------|------|
| | 1 Per Cent. | | | | 5 Per Cent. | | | | 20 Per Cent. | | | | 1 Per Cent. | | | | 5 Per Ct. | |
| Degree of Reaction. . . . | 0 | + | ++ | +++ | 0 | + | ++ | +++ | 0 | + | ++ | +++ | 0 | + | ++ | +++ | 0 | Pos. |
| Non-tuberculous Cases | 84 | 13 | 3 | 0 | 49 | 38 | 11 | 2 | 27 | 40 | 29 | 5 | 97 | 3 | 0 | 0 | 94 | 6 |
| Doubtfully Tuberculous Cases. | 64 | 32 | 4 | 0.5 | 35 | 49 | 13 | 3 | 18 | 39 | 29 | 13 | 87 | 7 | 5 | 2 | 75 | 25 |
| Probably Tuberculous Cases. | 46 | 51 | 3 | 0 | 14 | 51 | 31 | 4 | 6 | 26 | 40 | 28 | 69 | 14 | 14 | 3 | 39 | 61 |
| Incipient Tuberculous Cases. | 44 | 41 | 15 | 0 | 22 | 35 | 26 | 19 | 11 | 22 | 30 | 36 | 52 | 22 | 7 | 19 | 48 | 52 |
| Moderately Advanced Tuberculous Cases . . | 40 | 54 | 6 | 0 | 7 | 55 | 32 | 6 | 3 | 27 | 40 | 30 | 29 | 30 | 23 | 17 | 13 | 87 |
| Far Advanced Tuberculous Cases. | 54 | 40 | 6 | 0 | 24 | 38 | 32 | 6 | 9 | 35 | 26 | 30 | 31 | 27 | 31 | 11 | 14 | 86 |

ILLUSTRATING THE NUMBER PER HUNDRED OF REACTIONS TO THE
CUTANEOUS AND CONJUNCTIVAL TESTS IN 1,000 PATIENTS

| Strength of Tuberculin. | PER CENT. OF SKIN REACTIONS | | PER CENT. OF CONJUNCTIVAL REACTIONS | | | |
|---------------------------------------|-----------------------------|------|-------------------------------------|------|-------------|------|
| | Pure | | 1 Per Cent. | | 5 Per Cent. | |
| Degree of Reaction. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. |
| Cases: | | | | | | |
| Non-Tuberculous Cases. | 43 | 57 | 98.4 | 1.6 | 92 | 8 |
| Doubtfully Tuberculous Cases. | 17 | 83 | 85 | 15 | 64 | 36 |
| Probably Tuberculous Cases. | 7 | 93 | 60 | 40 | 27 | 73 |
| Incipient Tuberculous. | 6 | 94 | 31 | 69 | 14 | 86 |
| Moderately Advanced Tuberculous . | 3 | 97 | 23 | 77 | 8 | 92 |
| Far Advanced Tuberculous. | 8 | 92 | 33 | 67 | 17 | 83 |

Roepke's results agree with our own. Wolff-Eisner replies that he lacks confidence in the accuracy of Roepke's diagnosis since Roepke lays too much stress upon the confirmatory evidence of a constitutional reaction to subcutaneous injections of tuberculin. We have at some length discussed this point and our conclusions lead us to cordially agree with Wolff-Eisner. However, accepting only cases with tubercle bacilli in the sputum, our results re-

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main unaltered. These results force upon us the conviction that the occurrence and intensity of the conjunctival and cutaneous reaction depend in a measure upon the extent of the lesion.

The importance of the general condition of the patient we have sought to arrive at by classifying our cases in reference to their appearance and general bodily vigor at the time the tests were given. Such a classification is a rough one and its results are only applicable in a general way. A convincing conclusion could be reached only by studying the subsequent course of the disease in a large number of tested patients. This we are at present trying to do, but as yet cannot state what the outcome of the investigation will be.

ILLUSTRATING THE NUMBER PER HUNDRED OF REACTIONS TO THE CUTANEOUS AND CONJUNCTIVAL TESTS IN PATIENTS IN GOOD AND POOR GENERAL CONDITION.

| Strength of Tuberculin..... | PER CENT. OF SKIN REACTIONS | | | | | | | | | | | | PER CENT. OF CONJUNCTIVAL REACTIONS | | | | | |
|-----------------------------|-----------------------------|----|----|-----|-------------|----|----|-----|--------------|----|----|-----|-------------------------------------|----|----|-----|-----------|------|
| | 1 Per Cent. | | | | 5 Per Cent. | | | | 20 Per Cent. | | | | 1 Per Cent. | | | | 5 Per Ct. | |
| Degree of Reaction..... | Neg. | + | ++ | +++ | Neg. | + | ++ | +++ | Neg. | + | ++ | +++ | Neg. | + | ++ | +++ | Neg. | Pos. |
| Good general condition..... | 36 | 52 | 11 | 0 | 13 | 35 | 36 | 15 | 8 | 17 | 32 | 44 | 35 | 31 | 16 | 18 | 15 | 85 |
| Fair general condition..... | 45 | 49 | 6 | 0 | 12 | 55 | 28 | 5 | 6 | 34 | 33 | 27 | 33 | 30 | 24 | 13 | 9 | 91 |
| Bad general condition..... | 53 | 41 | 6 | 0 | 22 | 42 | 31 | 5 | 6 | 35 | 33 | 26 | 31 | 23 | 30 | 16 | 12 | 88 |

The following table shows that of 38 cases who died a short time after receiving the test only 10 per cent. failed to react to the cutaneous test and 26 per cent. to the conjunctival.

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ILLUSTRATING THE NUMBER PER HUNDRED AND SEVERITY OF REACTIONS IN THE CUTANEOUS AND CONJUNCTIVAL TESTS PERFORMED UPON INDIVIDUALS IN DIFFERENT STAGES OF THE DISEASE AND IN GOOD AND POOR GENERAL CONDITION.

| Strength of Tuberculin..... | PER CENT. OF SKIN REACTIONS | | | | PER CENT. OF CONJUNCTIVAL REACTIONS | | | | | |
|--------------------------------|-----------------------------|----|----|-----|-------------------------------------|----|----|-----|----------------|----|
| | Pure O. T. | | | | 1 Per Cent. O. T. | | | | 5 P. Ct. O. T. | |
| Degree of Reaction..... | - | + | ++ | +++ | - | + | ++ | +++ | - | + |
| 116 Favorable condition..... | 5 | 60 | 28 | 7 | 27 | 32 | 27 | 14 | 11 | 89 |
| 118 Unfavorable condition..... | 9 | 71 | 14 | 6 | 31 | 36 | 19 | 14 | 14 | 86 |
| 38 Died..... | 10 | 75 | 10 | 5 | 26 | 33 | 20 | 20 | 13 | 87 |
| 34 Incipient cases..... | 6 | 65 | 23 | 6 | 31 | 34 | 23 | 12 | 14 | 86 |
| 77 Moderately advanced..... | 3 | 61 | 26 | 10 | 23 | 33 | 24 | 20 | 8 | 92 |
| 186 Far advanced..... | 8 | 70 | 16 | 6 | 33 | 34 | 21 | 12 | 17 | 83 |

This divergence in the results obtained by Wolff-Eisner and by ourselves may perhaps depend upon differences in material and classification. Wolff-Eisner has worked with hospital patients, we with ambulant patients, and the German stage classification, particularly as regards the incipient class, is less exacting than the demands of the code recommended by the National Association, which we have followed. Therefore, Wolff-Eisner has had more moribund cases than have we and has no doubt included in his first stage group many cases which we would be obliged to place in the moderately advanced group. It should be remembered, too, that, according to the National Association classification, rapidly advancing and moribund cases of tuberculosis are no longer admissible to the moderately advanced group, even though the lesion itself be not extensive.

Aside from this difference in results we believe that Wolff-Eisner has exaggerated the importance of the deductions from even such figures as he presents. We must allow that, in patients with rapidly advancing lesions and in those worn out by years of struggle with the disease, the power to react tends to decrease and frequently is absent.

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However, we do not require the assistance of tuberculin reactions to inform us under these conditions what is the likely outcome. For tuberculin to aspire to prognostic dignity it must give us information that other methods of clinical observation do not bestow. In this regard we are convinced that it fails. Of two individuals with advanced pulmonary lesions it may indicate which is making the better fight against the disease, but other clinical methods give the same indication equally, if not more reliably. Of two individuals with moderately advanced disease and in equally good general condition, tuberculin cannot predict with more assurance than other clinical methods the state of affairs a year hence.

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We have already had occasion to refer to the remarkable results obtained by Römer¹ in the application of the intracutaneous tuberculin test in guinea pigs infected with tuberculosis. Römer has systematically tested guinea pigs infected with varying amounts of tubercle bacilli of different virulence by performing weekly intracutaneous tests. The test consists in injecting into the skin 0.1 c. c. of tuberculin dilutions representing 0.02, 0.002, 0.0002, 0.00002, 0.000002 c. c. tuberculin. The area of induration is measured after twenty-four hours with a caliper and compared with the thickness of the skin in an uninjected area. An animal reacting to 0.02 and not to 0.002 c. c. of tuberculin is said to have I grade of sensitiveness; one reacting to 0.002 and not to 0.0002, II grade of sensitiveness, etc. He has never observed sensitiveness to amounts less than 0.000,002 c. c., or grade V.

¹ Römer and Joseph: Zur Verwertung der intrakutanen Reaktion auf Tuberkulin. Beitr. z. Klin. d. Tuberk., 1909, xiv, 1.

Ibid.: Tuberkulose und Tuberkulinreaktion. Ibid., 1910, xvii, 449.

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By varying the amount and virulence of the cultures injected he has been able to study the variation in tuberculin sensitiveness during all grades of infection from rapidly fatal to mild ones ending in spontaneous recovery. Stated briefly, his results show that the more severe the infection the higher the grade of sensitiveness developed and the more quickly is this high point reached. Instances in which the disease remains localized show a strikingly low grade of sensitiveness. Should similar relations obtain in man, results of the greatest diagnostic and prognostic importance would follow. However, infection in man plays quite a different rôle from infection in guinea pigs, and the experimental data following experiments upon laboratory animals are not directly transferable to human pathology.

Ellermann and Erlandsen¹ have studied quantitative tests upon man. They perform the cutaneous test by applying a drop of 32 per cent., 8 per cent., 2 per cent., and 0.5 per cent. old tuberculin upon the skin and making through each dilution a superficial incision 2 to 3 cm. long. After two minutes the tuberculin is mopped off with cotton and a protective dressing applied. To insure a uniform depth of incision they use a lancet with adjustable point. At the end of twenty-four and forty-eight hours the diameter of the resulting papule is carefully measured and the mean of the readings taken. From the mean difference between the papules (D) and the estimated diameter of the 4-per-cent. papule (the mean of the four papules) they estimate the tuberculintiter or grade of sensitiveness of the individual. Thus:

¹ Ellermann and Erlandsen: Ueber quantitative Ausführung der kutane Tuberkulinreaktion und über die klinische Bedeutung des Tuberkulintiters. Deutsch. med. Wehnschr., 1909, xxxv, 436.

Ibid.: Über Sensibilisierung bei der kutanen Tuberkulinreaktion. Beitr. z. Klin. d. Tuberk., 1909, xiv, 43.

Erlandsen and Peterson: Untersuchungen über die diagnostische Bedeutung des Tuberkulintiters. Beitr. z. Klin. d. Tuberk., 1910, xvi, 291.

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| TUBERCULIN | 24 HOURS | 48 HOURS | AVERAGE | D | RESULT |
|------------|----------|----------|---------|-----|------------|
| 32% | 6.5 mm. | 7.2 mm. | 6.9 mm. | | |
| 8% | 4.6 " | 5.0 " | 4.8 " | 2.1 | P4=3.8 mm. |
| 2% | 2.2 " | 3.0 " | 2.6 " | 2.2 | D=2.0 " |
| 0.5% | trace | 1.0 " | 0.8 " | 1.8 | T=264 " |

From observations upon 547 patients (457 clinically non-tuberculous, 46 clinically tuberculosis suspected, and 44 definite cases), Erlandsen and Peterson draw a number of conclusions, chief among which are: 1. In each of the three classes the average degree of sensitiveness increases. The tuberculin titer, therefore, bears some relation to the grade of tuberculous infection. 2. There are so many individual variations in each group that one cannot diagnose tuberculous disease from the tuberculin titer alone. However, in conjunction with the general clinical symptoms it is a valuable indication. 3. In most instances of latent tuberculosis the tuberculin titer is under 100. A tuberculin titer of from 200 to 400 makes the presence of an active tuberculous focus probable. 4. When a tuberculous lesion has been present a tuberculin titer under 100 indicates that the disease is quiescent. In drawing this conclusion it must be borne in mind that acute infections temporarily diminish tuberculin hypersensitiveness. 5. There is a marked fall in tuberculin hypersensitiveness shortly before death and a similar fall during cachexia occasioned by chronic disease such as carcinoma.

A more extended use of Ellerman's method is necessary before a just appreciation of its value can be reached. His figures give rough indications rather than precise information and they themselves draw conservative conclusions. Although we have not ourselves employed the method our experience with the cutaneous test and its wide individual variations leads us to believe that they have applied exact mathematical calculations to factors of indeterminable variation. The results of v. Pirquet, of Lord, of Schütz

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and Vidéky and of Boardman indicate that a normal variation of at least 5 mm. must be allowed for papules occurring in tests performed as nearly alike as possible upon the same individual. There is also important individual differences in the thickness of the skin and its power of absorption. These two factors introduce variants which seriously compromise accurate mathematical deductions based upon them.

White and his co-workers have sought to make the cutaneous test even more delicate.¹ As their technique has undergone a number of changes, we quote from the latest publication. The inner surface of the forearm is cleaned with alcohol and ether and with the v. Pirquet scarifier an abrasion is made measuring 2 mm. in diameter, the base of which must show a bright pink color. Not the least drop of blood must be drawn, but it is essential that the pink color appear at the base. After having made the proper scarification a drop measuring exactly 0.01 c. c. of the tuberculin solution to be used is applied with a throttle pipette exactly over the point of scarification. This is then covered by a vaccine shield, kept in place by two strips of adhesive plaster, and the patient directed to hold the arm in a horizontal position for at least an hour, so as to prevent flowing of the drop. For the first test a 1-per-cent. tuberculin dilution is used. If this gives no reaction, after an interval of four days, a second test is made with a stronger solution; if too violent a reaction occurs to 1 per cent., a weaker solution is employed for the second test. In this manner one searches for the dilution to which the individual gives a minimal cutaneous reaction. A minimal cutaneous reaction

¹ White and Graham: A quantitative modification of the von Pirquet tuberculin reaction and its value in diagnosis and prognosis. *Jour. Med. Research*, 1909, xx, 347. Ibid.: An index to tuberculin treatment in tuberculosis by the minimal cutaneous reaction method. Ibid., 1909, xxi, 255. White and Van Norman: An individual quantitative basis for dosage in tuberculin treatment. *Tr. Nat. Assn. for the Study and Prevention of Tuberc.*, 1910, vi, 224.

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is defined as a reaction that gives a redness and swelling measuring four to six millimeters in diameter within seventy-two hours. When one is pressed for time two tests, with different strengths of tuberculin, always putting the weaker distal to the stronger, may be performed simultaneously. However, this procedure is inadvisable. White claims the greatest accuracy for this method and states that from the minimal cutaneous reaction he is able to unerringly state the exact dose which, administered subcutaneously, will produce a local reaction and the exact amount necessary to liberate a general reaction. While White has anticipated important diagnostic and prognostic inferences from the determination of the minimal cutaneous reaction by what he terms the volumetric quantitative method, he has not so far published a sufficient number of cases to convincingly demonstrate them. He states specifically only that an absence of reaction to a certain dilution is important evidence in excluding tuberculosis.

The results that we had obtained previous to White's publication by performing the cutaneous test with varying strengths of tuberculin were at variance with his conclusions. To determine to what extent technical differences might be held accountable for the variation, Boardman¹ studied the method.

To ascertain the degree of normal variation he performed two tests simultaneously upon 76 individuals. The same quantity of tuberculin, the same length of time allowed for absorption and the same technique were used in all. The total variation was 84 mm.; the average variation 1.1 mm.; the maximum variation 4.5 mm. To ascertain the influence of the size of the drop two tests were made simultaneously upon 63 individuals, using a small drop for one test and twice the amount of the same dilution for the other test. The technical factors were identical in all the tests.

¹ Boardman: Results unpublished.

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The total variation was 64.89 mm.; average variation, 1.03 mm.; maximum variation, 5.5 mm. As these variations are practically identical with the normal variations, it is just to conclude that, while the concentration of tuberculin is of the greatest importance in determining the severity of the reaction, the actual amount of tuberculin applied is within reasonable limit insignificant.

To ascertain the influence of the length of time the tuberculin is allowed to remain upon the skin, two tests were performed simultaneously upon 50 individuals. Two drops of tuberculin of the same size and strength were placed upon the skin and similar abrasions (incisions) made through both. One drop was mopped off at the end of 10 minutes, the other allowed to dry and protected with a vaccination shield for twenty-four hours. Total variation, 98 mm.; average variation, 1.96 mm.; maximum variation, 8.5 mm. This experiment shows that absorption is practically ended after 10 minutes and only slightly larger reactions occur when the tuberculin is allowed to remain upon the skin for twenty-four hours.

These results lead us to believe that White has placed more stress upon the actual size of the drop of the tuberculin and the length of time allowed for absorption than these factors deserve. The particular advantages claimed for his method would seem, then, to reside in the method of making the abrasion.

Boardman performed simultaneous tests upon 97 individuals, using for one an abrasion made with the v. Pirquet scarifier, for the other an incision made with a scalpel, all other conditions being the same. In 58 instances the reactions were practically equal; in 33 instances the incision reaction was more intense than the abrasion reaction; in 6 instances the abrasion reaction was more intense than the incision reaction.

Estimating the minimal cutaneous reaction strictly

QUANTITATIVE TUBERCULIN TESTS

according to White's directions, Boardman found no constant relation between the reaction and the extent of the disease, or the condition of the patient. However, only 42 cases were tested. In a few cases, subsequently given tuberculin subcutaneously, the size of the dose necessary to liberate a reaction did not bear a constant ratio to the minimal cutaneous reaction.

The table on page 176 shows the results we obtained by applying simultaneously tests with 1-per-cent., 5-per-cent. and 20-per-cent. tuberculin upon 530 individuals. To the 20-per-cent. dilution practically all of the tuberculous cases react and most of the apparently healthy. To the 5-per-cent. dilution fewer of the apparently healthy react, but likewise many of the tuberculous do not. To the 1-per-cent. dilution relatively few of the non-tuberculous react, but its diagnostic value is annulled by the small number of the tuberculous that react.

The real value of quantitative tuberculin tests cannot at present be estimated. Qualitative tests have been applied extensively enough to warrant deductions as to their significance, and the urgent immediate necessity is to have equally accurate and full data upon variations in quantitative relations. It is important to know if there is any constant variation in the degree of hypersensitiveness corresponding with the activity, extent and progress of the infection, how sensitiveness varies from week to week during the spread or arrest of a tuberculous focus and how it is influenced by tuberculin treatment. The results of Ellerman and Erlandsen bear suggestively upon the correspondence of activity and the degree of sensitiveness, and these are the only results we have at present to judge from.

For the various reasons previously stated, we look upon the cutaneous test as a relatively rough one, subject to wide individual variations and utterly unsuited for quantitative tuberculin tests. The intracutaneous test,

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though a little more troublesome, has such evident advantages over the cutaneous as an accurate quantitative test that it alone should be employed in determining the degree of hypersensitiveness. Extended application of the intracutaneous test is sure to throw valuable light upon the details of our knowledge of tuberculin hypersensitiveness. It is necessary to emphasize that in the intracutaneous test the concentration of the tuberculin solution is as important a factor as the actual amount of tuberculin introduced.

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Use of Tuberculin in the Diagnosis of Pulmonary Tuberculosis.—The diagnosis of pulmonary tuberculosis may, in certain instances, be made from the physical signs alone and in other instances from the symptoms alone, but usually it is a consideration of the history of the illness, together with the results of the physical examination, and of the clinical observations of symptoms that leads to an accurate conclusion.

In making routine examinations one not infrequently encounters individuals presenting evident signs of pulmonary disease, to whom the discovery is as astonishing as it is to the examiner. Such instances present no more difficulty in diagnosis than do those who come for examination on account of disturbing symptoms and in whom the physical signs obviously indicate pulmonary tuberculous disease. The physical signs of pulmonary tuberculosis may be simulated by pulmonary disease other than tuberculous, and perhaps it is not strictly justifiable to say that the tuberculous nature of the disease is ever obvious from the physical signs alone. Serious errors do follow such confident interpretation, but mistakes in this direction are rarely made by experienced observers.

Similar inferences may be drawn from the symptoms alone. A frank hemoptysis, even when physical signs of

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pulmonary disease are entirely absent, is still sufficient evidence for diagnosis if the presence of certain other diseases, as a rule easily excluded, can be ruled out. While hemoptysis, thus restricted, is the only single symptom pathognomonic of pulmonary tuberculosis, the occurrence of definite groups of symptoms warrants the deduction of an extremely probable diagnosis. Prolonged cough with evening elevation of temperature and loss of weight and strength is such a complex.

A combination of obvious physical signs and definite symptoms approaches the diagnosis still nearer to certainty. Tuberculin can add so little to this assurance that its use under such conditions is superfluous.

Absolute certainty in the diagnosis of pulmonary tuberculosis is reached only when tubercle bacilli are found in the sputum. The importance of this obvious statement has been lost sight of in our straining after earlier and earlier diagnosis. During the past ten years the sputum examination has lost its predominant position and has suffered in the thoroughness and minuteness with which it is carried out. Most of our clinical deductions are probability diagnoses, and while it would be folly to let treatment wait upon assurance, the value of complete confirmation in the study of disease cannot be too firmly emphasized or too eagerly striven for.

The success that has followed the treatment of pulmonary tuberculosis in its initial stage is the motive that has stimulated our efforts at early diagnosis. It is the exception to find tubercle bacilli in the sputum of individuals with beginning tuberculosis of the lungs, and our eagerness to detect the disease at its onset has led to the refinement of other methods of examination. This is particularly true of the arts of percussion and auscultation, which are at present applied to pulmonary diagnosis with a skill and accuracy never previously attained. The slightest deviation

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from normal conditions is recognized and even small lesions outlined with remarkable precision.

The earliest physical signs of tuberculous involvement of the lungs are in the majority of instances discovered at the apices. Their recognition is made difficult by the well-known normal difference in the auscultatory phenomena at the apices, a difference that displays wide individual variations. The clinical interpretation of definite but slight changes in apical physical signs is perplexing, since they do not necessarily indicate active tuberculous disease.

With the refinement of physical diagnosis has come a tendency to rely too implicitly upon the data it furnishes and to disregard the equal importance of clinical symptoms. Our own experience in this direction has been extremely interesting. When the special tuberculosis dispensary was started at the Johns Hopkins Hospital seven years ago, those of us who worked there had the usual training in pulmonary examination that comes from some years' work in hospital and dispensary. By constant application we gradually developed the skill to elicit abnormal physical signs that had previously been overlooked. The recognition of such slight physical signs led to the diagnosis of pulmonary tuberculosis, regardless of the presence or absence of symptoms, admission to the sanatorium was urged and the results of treatment were most gratifying. Confidence in the correctness of the conclusion was enhanced by the confirmatory evidence lent by tuberculin. Of the first thirty-six patients who received tuberculin subcutaneously, all but one reacted. Slight physical signs and the tuberculin reaction played so smoothly together that we finally became suspicious and began to administer tuberculin subcutaneously to a large number of individuals with no evidence of pulmonary tuberculous disease. To our dismay most of these patients likewise reacted, and it was only the

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subsequent extensive application of the local tuberculin reactions that convincingly demonstrated the frequent occurrence of tuberculin hypersensitiveness in the absence of clinical tuberculous disease. The objective reality of the slight abnormal physical signs discovered has been fully established by parallel physical and X-ray examinations.¹ Slight dulness and minor changes in the character of breath sounds are always associated with shadows of increased density in the X-ray plates. Their existence can no longer be ignored as superfluous refinements, nor be discarded as coming within the range of normal variation.

Accepting them, then, as the expression of real changes in the lung tissue and granting that such changes are for practical purposes almost always the result of tuberculous infiltration, they are still, taken alone, insufficient evidence upon which to base a diagnosis of active tuberculous disease. The routine examination of medical students, of applicants for the Training School for Nurses and of the healthy members of tuberculous families has demonstrated that, roughly, twenty per cent. of apparently healthy adults present such minor abnormal physical signs. During the past few years we have ceased to regard such individuals as definitely tuberculous and have become far more conservative in urging them to avail themselves of sanatorium treatment. Numerous patients displaying abnormal apical physical signs have, in the absence of definite symptoms, been allowed to continue to live under customary surroundings and but a small number have subsequently developed obvious signs of active pulmonary disease. In assuming such a conservative attitude we run the risk of postponing treatment where it may be seriously needed, but so large a number of individuals is spared the inconvenience and

¹ Dunham, Boardman and Wolman. The stereoscopic X-ray examination of the chest, with especial reference to the diagnosis of pulmonary tuberculosis. *Johns Hopkins Hosp. Bull.*, 1911, xxii, 229.

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expense of prolonged absence from home and employment that to us the risk seems entirely justified. In the presence of these minor physical signs we look to a careful investigation of the symptoms to decide whether the process be active or inactive. Where these fail to give a definite decision tuberculin may render further assistance.

In the diagnosis of pulmonary tuberculosis tuberculin is of value in gaging hypersensitiveness and in eliciting focal reactions. Tuberculin hypersensitiveness is never decisive information, it can only add another link to the chain of diagnostic evidence. This, we believe, we have already made quite clear. A focal reaction, on the other hand, tells definitely of the presence of disease and something, at least, of its extent. Naturally we have striven to reach such certainty in tuberculin diagnosis but our efforts have not met with signal success.

The evidences of a focal reaction in the lungs consist of changes in the symptoms and in the extent and character of the physical signs. Pain in the chest and increased cough and expectoration are the principal symptoms. Occasionally tubercle bacilli appear in the sputum when they have previously been absent. The occurrence of pain in the chest and increased cough and expectoration during a constitutional reaction, while extremely suggestive, are not alone sufficient to definitely conclude that a focal reaction in the lungs has occurred. To be certain of its occurrence there must be changes in the physical signs.

The relative number of focal reactions that are discovered will depend upon the class of patients receiving the injections and the standard one adopts in deciding what changes in the physical signs constitute satisfactory evidence of a focal reaction. Otten discovered focal reactions in 68 per cent. of 324 patients reacting to tuberculin. Roepke in 718 patients obtained focal reactions in 45 per

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cent. of those who reacted.¹ Of 113 patients reacting constitutionally to tuberculin we obtained evidence of a focal reaction in 22, or 19 per cent. In our own experience we have obtained fewer focal reactions as our skill in physical diagnosis has increased. Some explanation must be offered for such widely different results. We have ourselves come to rely solely upon the occurrence of râles which had previously been absent and which again disappear as the reaction subsides as evidence of a focal reaction.

Otten's² report comprises 324 cases from the medical clinic at Tübingen. The doses administered were 0.1, 0.5, 1.5 and 10 mg.

| | |
|------------------------------------------------------------|------------------|
| Focal and general reactions were obtained in 197 instances | = 60.8 per cent. |
| Focal reactions alone were obtained in..... 24 | " = 7.4 " |
| General reactions alone were obtained in.... 76 | " = 23.5 " |
| Focal and general reactions both absent in.. 27 | " = 8.3 " |

All of the cases had symptoms and most of them slight physical signs suggesting the presence of pulmonary tuberculosis, but in none were the symptoms and signs alone sufficient to warrant a definite diagnosis. We would call attention to the report of 24 instances of focal reactions without constitutional symptoms—an unusual occurrence. Of the cases exhibiting a focal reaction the following signs were considered sufficient to warrant the deduction:

| | |
|--------------------------------------------------|---------|
| The appearance of dulness previously absent..... | 6 cases |
| Increase of preëxisting dulness | 78 " |
| Appearance of dulness with fresh râles..... | 3 " |
| Increase of dulness with fresh râles..... | 66 " |
| Dulness and râles both increased..... | 10 " |
| Dulness unchanged, fresh râles..... | 40 " |
| Dulness unchanged, râles increased..... | 9 " |
| Normal percussion note, râles increased..... | 9 " |
| | 221 " |

¹ Roepke: Über diagnostische Tuberkulindosen. Ztschr. f. Tuberk., 1907, x, 412.

² Otten: Ueber die Herdreaktion bei der subkutanen Tuberkulinprobe und ihre Bedeutung für die Frühdiagnose der Lungenspitzen-tuberkulose. Med. Klin., 1910, vi, 1089.

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It is apparent what an important place Otten gives to percussion in the discovery of focal reactions. He says in order to appreciate the changes one must have a perfect mastery of the art of percussion. Indeed we agree that one must, and, while we are lost in admiration of his skill, we humbly confess that, though we have practiced the art assiduously, such finesse is quite beyond our attainment.

Roepke is willing to decide upon changes in the character of the breath sounds as sufficient evidence of the occurrence of a focal reaction, a standard that we look upon as unsatisfactory and misleading. It introduces too obviously the individual factor, and we are, after careful study, unwilling to draw such far-reaching conclusions from apparent changes in the intensity and quality of the breath sounds. We have further observed that although an increase in the number of existing râles commonly enough occurs during a constitutional reaction to tuberculin, it but rarely happens that râles appear where they have previously been absent. The presence of definite moist râles is, however, by itself such conclusive evidence of the existence of an active tuberculous focus that tuberculin is seldom needed to confirm the diagnosis. When râles are absent and the decision of an active or inactive lesion rests largely upon the outcome of the tuberculin test, conclusive signs of a focal reaction seldom occur.

Because of the frequent failure to yield indications in the one direction in which the results are decisive, we cannot urge the subcutaneous test as the most generally useful in the diagnosis of pulmonary tuberculosis. As indicators of tuberculin hypersensitiveness the local tuberculin reactions are equally reliable and far more simple. We have discussed in detail the clinical significance of the various reactions. For practical purposes we prefer the cutaneous and conjunctival tests, performed simultaneously. When both tests are positive they are strong confirmatory

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evidence of the presence of an active tuberculous lesion; when both are negative they exclude with reasonable assurance the presence of an active tuberculous lesion; when the conjunctival test is negative, the cutaneous positive, we are thrown back unaided upon our other clinical resources. Occasionally the intracutaneous or the subcutaneous-local test may be desirable to exclude still more surely than the cutaneous test does the presence of a tuberculous focus. In selected cases where it is advisable to attempt the production of a focal reaction the subcutaneous test is indispensable.

Tuberculin may be of assistance in the diagnosis of pulmonary tuberculosis under two conditions:

1. Where there is a definite pulmonary lesion the tuberculous nature of which is a question. In such instances a high grade of tuberculin hypersensitiveness clinically manifested by a definite reaction to the 1-per-cent. conjunctival test adds important evidence in favor of its tuberculous nature. A negative cutaneous test more probably still excludes tuberculosis as the etiological factor. It is not necessary to rehearse again the conditions under which a tuberculin reaction may be absent, although the individual harbors a tuberculous lesion, nor to quote statistical confirmation of these deductions. For such evidence the reader is referred to the sections on the results obtained from the application of the various tests. We have said that focal reactions occur far more frequently when definite signs of a pulmonary lesion are present than in their absence. In these questionable cases, then, the subcutaneous test finds its most important application, since a definite focal reaction is more valuable information than that obtained from hypersensitive tests alone. However, it should be emphasized that the subcutaneous test should be given with the sole object of producing a focal reaction. A constitutional reaction to the subcutaneous test is by no means such

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strong confirmatory evidence as a positive 1-per-cent. conjunctival test, and a failure to react to the subcutaneous test is of no more excluding value than a negative cutaneous test.

2. When the symptoms suggest the presence of a pulmonary tuberculous focus and only indefinite physical signs are found. In such instances, as far as our experience goes, the manifestations of focal reactions to subcutaneous injections of tuberculin but seldom occur. Since a positive conjunctival reaction has far more clinical significance than a constitutional reaction to tuberculin and a negative cutaneous test is approximately equivalent in significance to a negative subcutaneous test, we prefer as a routine to give the cutaneous and conjunctival tests simultaneously and to reserve the subcutaneous test to meet special conditions making an attempt at producing a focal reaction desirable.

It must be granted that there is a serious objection to this plan. Whether the conjunctival test has been positive or negative, there is a marked tendency for the conjunctiva to react upon subsequent subcutaneous injections of tuberculin. These flare-ups or secondary reactions are often severe and, since they may occur after the injection of doses of tuberculin too small to liberate a general reaction, they may make it inadvisable to push the subcutaneous test further. A previous conjunctival test may, therefore, render it impossible to subsequently elicit a focal reaction. Where the conditions make the production of a focal reaction desirable it is always best to administer the subcutaneous test first. Should the conjunctival test have already been given we may proceed with the subcutaneous test, but occasionally we will be forced to abandon it before completion on account of the intensity of the associated conjunctival reaction.

Use of Tuberculin in the Diagnosis of Bone, Joint, and

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Glandular Tuberculosis.—We have emphasized that whenever it is possible to elicit a focal reaction the subcutaneous tuberculin test is to be performed, since a focal reaction is of far more value in diagnosis than are the results obtained from hypersensitive reactions alone. Baer and Kennard¹ have demonstrated the almost constant occurrence of focal reactions about tuberculous bone and joint lesions during a general reaction to tuberculin and depending largely on their experience we urge the manifest advantage of the subcutaneous test over the local tests in the diagnosis of bone and joint tuberculosis. The signs of a focal reaction consist of increased redness, swelling, heat and pain, with more evident limitation of movement and the appearance or increase of crepitus. In spinal lesions exaggeration of the nervous symptoms may occur. It is important to emphasize that the failure of definite signs of a focal reaction to occur does not necessarily exclude the possibility of the lesion under investigation being tuberculous.

In bone and joint tuberculosis the local reactions are more valuable than in pulmonary tuberculosis, since as a rule hypersensitiveness is particularly well developed and the patients are more commonly in the early years of life when latent foci are less frequent. As already so often pointed out, a negative cutaneous test will, under appropriate conditions, exclude with reasonable probability the presence of a tuberculous focus. A positive conjunctival test will indicate the presence of an active tuberculous lesion, leaving it to other clinical symptoms and signs to decide its location. If there are evident signs of disturbance in a joint and no symptoms pointing to disease in other regions of the body, the conclusion is justified that the joint lesion is tuberculous. Such a conclusion must,

¹ Baer and Kennard: Diagnostic value of tuberculin in orthopedic surgery. Johns Hopkins Hosp. Bull., 1905, xvi, 13.

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however, be drawn with a certain reservation. It is quite possible that there may be a hidden tuberculous focus elsewhere in the body, for instance in the mediastinal glands, and, although the patient reacts to tuberculin, the particular lesion under investigation be not tuberculous. Failure to take this contingency into account has led to errors which are cast as compromising reflections upon the value of tuberculin in diagnosis. It cannot be too often pointed out that tuberculin hypersensitiveness indicates broadly only tuberculous infection and never by itself stamps any particular lesion as tuberculous. This is the business of clinical inference to which the tuberculin tests add considerations of value.

In children a constitutional reaction to the subcutaneous injection of tuberculin is more valuable evidence of the presence of an active tuberculous focus than in adults. There is, therefore, not the same discrepancy between the results of the subcutaneous and the conjunctival tests and the latter has not the manifest advantages it has in adult life. For children particularly the subcutaneous test is, then, decidedly preferable. Its results may be interpreted as follows:

1. A focal reaction makes the diagnosis of tuberculous bone or joint disease certain.

2. An absence of reaction to the subcutaneous test excludes, with the highest probability, the presence of tuberculous disease.

3. A positive constitutional reaction to the subcutaneous test unaccompanied by satisfactory signs of a focal reaction is still valuable evidence in favor of the tuberculous nature of the lesion and its value is greater the younger the child.

While the majority of orthopedic surgeons are agreed that focal reactions to the subcutaneous test are common in joint and bone tuberculosis, all have not obtained such

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favorable results. Frazier and Biggs,¹ for instance, claim to have missed them. Stern,² in a report of 471 cases in which tuberculin was used as an aid in diagnosis, advocates the simultaneous performance of the conjunctival and cutaneous test, according to the method we have outlined for pulmonary cases. Both tests positive indicates active tuberculosis, both negative reasonably excludes tuberculosis. When the cutaneous test is positive and the conjunctival negative, he employs the subcutaneous-local or intracutaneous tests, with very small doses of tuberculin as a further aid in diagnosis. Focal reactions are not sought. Of the 471 cases, the indications of the tuberculin tests, together with the clinical evidence, led to a correct diagnosis in all but six instances. In these six instances the error was a positive one, that is, tuberculosis was indicated where it did not exist. Wilms³ contends that fungus forms of joint tuberculosis are frequently unassociated with general tuberculin hypersensitiveness and that a negative cutaneous reaction does not exclude its presence.

In our experience glandular tuberculosis does not, as a rule, give striking signs of a focal reaction. In some instances there are increased pain, swelling and redness. On the whole, we feel that the local reactions are of more value in the differentiation of suspected glandular swelling than the subcutaneous test.

Use of Tuberculin in the Diagnosis of Genitourinary and Pelvic Tuberculosis.—We have emphasized frequently enough the superiority in diagnosis of focal reactions over hypersensitive tests and whenever a tuberculous lesion is situated favorably for the appreciation of focal changes the subcutaneous method is the test to be preferred. The fre-

¹ Frazier and Biggs: Cit. Baer and Kennard, loc. cit., p. 240.

² Stern: Tuberculin in orthopedic diagnosis. *Am. Jour. Orthop. Surg.*, 1911, ix, 25.

³ Wilms: Behandlung der Kehlkopftuberkulose mit Röntgenstrahlen (Tiefenbestrahlung). *Deutsch. med. Wehnschr.*, 1910, xxxvi, 259.

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quency with which demonstrable changes occur in renal, vesicle and pelvic tuberculosis varies widely, according to different authorities. The changes are seldom objectively appreciable and the interpretation depends upon the symptoms, pain, swelling, increased secretion, bleeding, increased frequency and pain on urination, etc. Again we must warn that the absence of focal changes during a constitutional reaction does not exclude the tuberculous nature of the suspected lesion. Birnbaum¹ has obtained the most satisfactory results with the subcutaneous test in the diagnosis of pelvic tuberculosis. In 100 cases all but one corresponded ultimately with the indications furnished by the test. Birnbaum emphasized the importance of symptoms referable to a focal reaction. Prochowneck likewise looks upon them as of frequent occurrence and positive in their indication. Pankaw² has not had such favorable results. In six of 22 cases no tuberculosis was found at operation, although the test had been positive. Three of these cases had complained of symptoms pointing to a focal reaction. Three cases with pelvic tuberculosis had no symptoms of a focal reaction during the general reaction.

The results of the hypersensitive test must always be interpreted with reserve. They never make a diagnosis, but merely furnish additional evidence for or against the tuberculous nature of the condition under consideration. Thus a positive reaction does not indicate necessarily that a renal, vesical or pelvic lesion is tuberculous, for, although these lesions be simple inflammatory diseases, a tuberculous focus elsewhere in the body may stimulate the hypersensitiveness that occasions the reaction. In this way are explained the

¹ Birnbaum: Die Erkennung und Behandlung der Urogenitaltuberkulose mit der Koch'schen Tuberkulinpräparaten. Zentralbl. f. Gynäk., 1907, xxxi, 1174.

² Pankaw: Discussion of Birnbaum. Ibid., p. 757.

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disappointing results obtained by Casper¹ and Karo² and others with the conjunctival test. The interpretation put upon the cutaneous and conjunctival tests in the diagnosis of pulmonary tuberculosis applies equally to tuberculous lesions elsewhere in the body.

Necker and Paschkis³ obtained valuable confirmatory evidence with the conjunctival test. Of 17 cases of surgical tuberculosis all but two cases reacted. One of these at autopsy proved to be carcinoma, the other was an advanced case of tuberculous peritonitis. Of 23 clinically non-tuberculous cases only 3 reacted. Of 15 urological cases suspected of having tuberculosis, 6 reacted and these subsequently proved to be tuberculous. The nine negative cases were also negative to other methods of investigation, including animal inoculation. Hörrmann⁴ did not obtain such a marked coincidence in his series. Of 4 definite cases all reacted; of 44 suspected cases 21, or 48 per cent., reacted; of 77 non-tuberculous cases 24, or 31 per cent., reacted. He lays more emphasis upon the excluding value of the negative test than upon the value of the positive reaction in indicating active tuberculosis.

Use of Tuberculin in the Diagnosis of Laryngeal Tuberculosis.—Tuberculin finds but a limited use in the diagnosis of laryngeal tuberculosis. Tuberculosis of the larynx is usually a complication of advanced pulmonary tuberculosis and the physical signs and the sputum examination are usually sufficient to settle the diagnosis. In most instances, too, the lesion itself has quite a characteristic appearance. It is only occasionally, then, that the diagnosis

¹ Casper: Verein f. i. Med. Berlin, January 20, 1908.

² Karo: Kritische Bemerkungen zur funktionellen Nierendiagnostik. München. med. Wehnschr., 1904, li, 122.

³ Necker and Paschkis: Die diagnostische Verwertbarkeit der Konjunktivalreaktion in der Urologie. Wien. klin. Wehnschr., 1908, xxi, 316.

⁴ Hörrmann: Die Konjunktivalreaktion bei genital Tuberkulose. München. med. Wehnschr., 1908, lv, 1375.

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of tuberculous laryngitis remains in doubt. The differentiation, as a rule, lies between tuberculosis and syphilis. As the larynx is so favorably situated for direct inspection, focal reactions are easily discerned. For this reason when the nature of a laryngeal lesion is in question the subcutaneous test should always be employed. The frequent occurrence of focal reactions is attested by Fränkel,¹ who has had a large experience with tuberculin in laryngeal lesions. Wolff-Eisner² advocates applying weak dilutions of tuberculin directly to the larynx and gradually increasing the dose until a focal reaction is obtained. The method has not been tried in practice.

The Use of Tuberculin in the Diagnosis of Cutaneous Tuberculosis.—Again in the diagnosis of doubtful cutaneous lesions the attempt at the production of a focal reaction takes precedence over hypersensitive tests. It will be remembered that it was from the changes occurring in lupus following subcutaneous injections of tuberculin that Koch drew his first classical picture of the focal reaction. From the earliest tuberculin diagnosis era up to the present time the subcutaneous test has furnished some of its most brilliant results in cutaneous lesions. The focal reaction is usually striking and unmistakable, although occasionally in old chronic lesions changes about the focus may fail to occur during the constitutional reaction. We have already spoken of the focal changes following the direct application of the cutaneous or percutaneous test to the suspected area. In performing the cutaneous test the abrasion is made directly into the diseased focus. It is best not to use pure tuberculin for the first test, since the reaction may be needlessly severe. Weaker dilutions, for example 1 per cent., should be used and, if necessary, the strength gradually

¹ Fränkel: Discussion. Berl. klin. Wehnschr., 1908, 672.

² Wolff-Eisner: Frühdiagnose und Tuberkulose-Immunität. 2nd edition. Würzburg, 1909, p. 151.

raised. It is said¹ that in lupus the skin is unusually sensitive for tuberculin, so that, though the conjunctival test is frequently negative, still the cutaneous reaction may be prompt and severe.

The Use of Tuberculin in the Diagnosis of Tuberculosis of the Eye and Ear.—There are practically no reports of the use of tuberculin in diseases of the ear. As in laryngeal lesions, the condition is usually easily diagnosed, particularly since tuberculosis of the middle ear occurs chiefly in the late stages of pulmonary tuberculosis. When pulmonary tuberculosis is present, tuberculin can give little aid in diagnosis, since the hypersensitiveness may depend upon the pulmonary lesion and in the presence of extensive pulmonary disease one should avoid giving large doses of tuberculin subcutaneously, for fear of a severe focal reaction in the lungs. In the few instances in which the diagnosis is in doubt, and examination fails to reveal a tuberculous infection elsewhere in the body, tuberculin may be of value. If the membrane is ruptured and the middle ear visible, the subcutaneous test is to be preferred, given with the intention of eliciting a focal reaction. When there are no manifest tuberculous lesions elsewhere in the body, a positive conjunctival reaction will be of some value in confirming a diagnosis. A negative cutaneous or subcutaneous test will be important evidence in excluding tuberculosis unless the patient has advanced tuberculous lesions elsewhere.

We have emphasized that any inflammatory disease and especially tuberculous disease of the eye contraindicates the application of the conjunctival test. Wolff-Eisner² has suggested instilling very dilute solutions into the conjunctival sac and to gradually increase the strength in an at-

¹ See Wolff-Eisner: *Frühdiagnose und Tuberkulose-Immunität*. 2nd edition. Würzburg, 1909, 126.

² *Ibid.*, p. 148.

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tempt to elicit a focal reaction. In this way serious focal reactions may be avoided. Erlanger¹ has obtained valuable results with a 1 to 10,000 dilution but the method has not been sufficiently employed to insure its trustworthiness.

The value of the subcutaneous tuberculin test in ophthalmological diagnosis has been emphasized by v. Hippel² and numerous other observers. Schoeler³ and Brons⁴ lay special importance upon the frequency, value and harmlessness of focal reactions.

In the presence of a conjunctival or intraocular inflammatory disease suspected of being tuberculous, the best procedure is to give a preliminary cutaneous test. If this is negative the tuberculous nature of the lesion is rendered improbable. If the test is positive, the subcutaneous test should then be given. Failure to react to five or ten milligrams practically excludes tuberculosis; the occurrence of a definite focal reaction establishes the diagnosis; a constitutional reaction to the subcutaneous injections unaccompanied by a focal reaction makes the tuberculous nature of the lesion highly improbable. When the ocular inflammation is acute and very severe it is inadvisable to attempt the production of a focal reaction.

The Use of Tuberculin in the Diagnosis of Serous Membrane Tuberculosis.—Tuberculous meningitis is never a primary disease and is usually but one localization of a generalized infection. The illness, under these conditions, takes its name from the mark which the prominence of the meningeal symptoms gives to the clinical picture. This

¹ Erlanger: Ueber konjunktivale Tuberkulinreaktion (sog. Ophthalmoreaktion) bei Augenkranken. *Ztschr. f. Augenheilk.*, 1908, xix, 450.

² v. Hippel: *Wirksamkeit des Kochschen Heilmittels*. Berlin, 1891.

³ Schoeler: *Erfahrungen über die Anwendung des Alttuberkulins zu Heilzwecken in der Augenheilkunde*. *Klin. Jahrbuch*, 1910, xxii, 173.

⁴ Brons: Ueber Ophthalmoreaktion. *Klin. Monatsbl. f. Augenh.*, 1908, xlv, 60; cited Wolff-Eisner: *Frühdiagnose und Tuberkulose-Immunität*. Würzburg, 1909, p. 148.

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explains the well-known failure of tuberculin to render valuable assistance in the diagnosis. When the presence of a tuberculous meningitis is in question one would obviously never set about to induce a focal reaction and, indeed, as we have previously explained, tuberculin hypersensitivity is usually absent in such acute, generalized forms of the disease. The subcutaneous test is excluded, since the usual presence of fever makes an accurate interpretation impossible and on account of the dangers of a focal reaction. The cutaneous and conjunctival tests are usually negative and are, therefore, of no value in excluding tuberculous meningitis. In adults a positive conjunctival reaction and in young children a markedly positive cutaneous test will lend support to the diagnosis.

Tuberculous pericarditis, like tuberculous meningitis, is never a primary disease, but, unlike tuberculous meningitis, the process is often localized. Frequently the disease is a direct infection from tuberculous mediastinal lymph glands. If the process is acute and accompanied by marked constitutional symptoms, tuberculin is of no more aid in the diagnosis than in meningeal tuberculosis. Again only a positive reaction will be of value, a failure to react by no means excluding tuberculosis. In cases with less pronounced or absent constitutional symptoms a negative result to the subcutaneous or cutaneous test will be important evidence against the disease being tuberculous, but even under these conditions absence of reaction should always be interpreted with reserve.

It has been rather a noteworthy feature of the tuberculin tests that tuberculous pleurisy, dry or with effusion, unaccompanied by evident pulmonary disease, frequently are associated with a low grade of tuberculin hypersensitivity. In a large proportion of cases of pleurisy with effusion the conjunctival test is negative and the cutaneous test but mildly positive. It is, as a matter of fact, but sel-

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dom that we need to resort to tuberculin to clear up a diagnosis of tuberculous pleurisy. The ordinary clinical indications are in nearly all instances sufficient. A positive conjunctival test will lend valuable support to the diagnosis; a negative cutaneous or subcutaneous test will speak against it, unless fever and constitutional symptoms are present. Bandelier and Roepke¹ claim that in dry pleurisy increased pain and more pronounced and extensive friction may occur during a constitutional reaction to the subcutaneous test and indicate a focal reaction.

Tuberculous peritonitis is one of the conditions in which the tuberculin tests have frequently failed to yield the proper indication. In acute cases or when the peritonitis is only one localization of generalized disease, hypersensitiveness is usually absent. A positive reaction in these cases will be important diagnostic information, but a negative reaction has no value in excluding tuberculosis. In more chronic or at least less virulent types of the disease, particularly in the instances coming on insidiously with little or no constitutional disturbance, tuberculin will lend valuable aid in diagnosis. The subcutaneous test is seldom advised in suspected tuberculous peritonitis. In chronic forms of the disease abdominal pain, distention, tenderness, vomiting and diarrhea are said to be the marks of a focal reaction.

It may be well, in conclusion, to emphasize once more that the tuberculin tests never in themselves establish a diagnosis. They are relative only to the other clinical symptoms and are valuable merely in so far as they point for or against a given conclusion. They add another factor to the probability in the case and, while all the evidence may approach our conclusion to certainty, it can never be said that tuberculin itself indisputably settles a diagnosis.

¹ Bandelier and Roepke: *Lehrbuch der spezifischen Diagnostik und Therapie der Tuberkulose*. 4th edition. Würzburg, 1910, p. 110.

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Were we to exclude all other evidence and accept only the conclusion based upon tuberculin diagnosis, we would come to sad havoc in our practice. He receives most from tuberculin who is best practiced in the ordinary arts of clinical investigation and who has trained his judgment to be patient and cautious.

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Can the use of tuberculin for diagnosis be fraught with any danger? Let us first consider the subcutaneous method of administration, because it is by this method that we obtain the constitutional reactions and the focal changes. The constitutional symptoms may be most severe, and may demand anodynes, soporifics, or stimulants, but no fatalities have been known to occur, unless the tuberculin was employed in individuals in whom it was obviously contraindicated. The constitutional reaction should be avoided when the patient is evidently already near his end, especially from cardiac or nephritic failure. Pauly,¹ for instance, reports a bad result from a reaction in a patient whose heart was already failing. The dangers from the constitutional reaction may be dismissed after the above-stated obvious warning.

It is around the focal effects that most of the discussion has ranged. That focal changes do occur has already been stated, and these will be further discussed in the section on Treatment. It is conceded that hyperemia with some degree of softening may occur. More often it is principally a hyperemia, but Baumgarten² and Baldwin, and others, have demonstrated a softening of the reacting

¹ Pauly: II Versamml. der Tuberk. Ärtz, Berlin, 1904.

² Baumgarten: Über die Einwirkung des Kochschen Mittels (Tuberkulin) auf die Impftuberkulose der Kaninchen. Internat. Beiträge zur wissenschaftl. Medizin, III. Festschr. f. Virchow, Berlin, 1891.

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focus. With such softening it is conceivable that resorption of toxic or infectious material is possible, or that contiguous extension may result. Or a rupture into a contiguous cavity might theoretically result, e. g., into a bronchus, or into the pericardial or pleural sac. Ziegler¹ describes a pericardial sac which looked as if a tuberculous focus might have ruptured into it, and Fränkel² cites a latent intestinal ulcer which, in a patient being treated by tuberculin, perforated intraperitoneally, causing a disseminated peritonitis. Ziegler, therefore, argues that there is more danger from the softening of internal lesions than from surface ones. Liebmann³ claimed to have evidence that tubercle bacilli may, during a reaction, gain access to the general blood-stream, but this claim has been successfully contradicted by Kossel,⁴ Baldwin⁵ and others. It is now generally agreed that there is no danger of dissemination through the blood-stream. But it is true that certain pathological material points to the possible contiguous extension of a lesion during a reaction, and it must be admitted that, although the usual result of a reaction is to wall off the focus, yet, when the hyperemia is excessive, contiguous extension seems plausible. However, autopsy material is not conclusive, since the tuberculosis in the cases reported was probably generalized even before the test was administered. We must resort to the clinical evidence. The subcutaneous test has been widely used for years, and the opinion of those who use it most is that

¹ Ziegler: See section on Treatment, p. 255.

² Fränkel: Aus der Univ. Poliklinik für Hals- und Nasenkrankheiten. Klin. Jahrb. Ergänzungsband, 1891, 258.

³ Liebmann: Ueber Tuberkelbacillen im Blute von Kranken, die mit Tuberkulin behandelt werden. Ber. klin. Wehnschr., 1891, xviii, 97, 393.

⁴ Kossel: Nochmals über den angeblichen Befund von Tuberkelbacillen im Blut nach Koch'schen Injectionen. Berl. klin. Wehnschr., 1891, xviii, 470.

⁵ Baldwin: The rational application and value of specific treatment for tuberculosis. Jour. Am. Med. Assn., 1904, xliii, 1600.

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there is practically no clinical evidence of the extension of a lesion during a reaction. We can reconcile this universal feeling upon the part of those using tuberculin extensively, with the isolated adverse cases, by remembering that the use of subcutaneous tuberculin in diagnostic doses has been more and more restricted to very slight lesions. In the early days this was not so. Not only are the lesions at present selected for such tests smaller, but the doses now given are not so abruptly large. In view of these two essential differences, we can credit the testimony of those using tuberculin largely, while not denying whatever pathologic evidence has been brought of adverse results. As regards the focal reaction in very slight pulmonary lesions (and only such should be subjected to the test), Köhler¹ admits that the reactive cough disappears quickly, and that only rarely does a negative sputum become positive. Brown,² too, testifies that there is no connection between the appearance of tubercle bacilli in the sputum and the increase of pulmonary symptoms. Minor³ also feels convinced of the safety of the test, when judiciously restricted to really doubtful cases. As regards pulmonary tuberculosis, then, we may say that if the lesion is really slight and dubious, if a diagnosis cannot be arrived at in any other way, and if it is necessary for a diagnosis to be made, the test may be conscientiously undertaken. But if the above conditions do not coexist there is no reason to subject the patient to even improbable dangers.

When tuberculosis of the brain or the meninges or of organs closely related to them—as the internal eye, ear, or nose—is suspected, it is best not to stir up a focal reaction as, in the first case, increased intracranial pressure

¹ Köhler: *Tuberkulin u. Organismus*. Jena, 1905, p. 41.

² Brown: The specificity, danger, and accuracy of the tuberculin tests. *Am. Jour. Med. Sc.*, 1911, cxlii, 469.

³ Minor: *Klebs, Tuberculosis*.

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may result, and in the latter a possible extension to the meninges. (Nourney.¹ Falkenberg.²)

If there is a large growth in the larynx, one must guard against stenosis resulting from the possible swelling.³

In tuberculosis of the joints, bones, or superficial glands the proceeding is safe, since even a slight focal reaction is visible. For this reason the first dose should be quite small. It is important, however, that, in testing any one joint or area for tuberculosis, the existence of active tuberculosis in the lungs, or elsewhere, should be excluded; this warning holds also for the diagnosis of tuberculous laryngitis.

There is no danger from the local reaction. Erysipelas⁴ has been reported, but this is due to uncleanly methods.

Since in the therapeutic use of tuberculin only the minutest doses are employed, and all but the minutest reactions are avoided, all the pathological data above quoted are not pertinent. In other words, the dangers attending large reactions do not enter into the question at all. We must, however, decide whether there is any cumulative effect that is in any way undesirable. It goes without saying that, if such is the case, the results of treatment would not be fortunate; but the evidence, however—as will be shown—is happily quite the other way. Moreover, there is no detailed evidence of any harm done by such doses, even to single organs. The urine, after large diagnostic doses, shows a transient albuminuria,⁵ but after therapeutic doses Denys finds that this never occurs. Brown⁶

¹ Nourney: Cit. Köhler.

² Falkenberg: Ein Beitrag zur Pathologie und Therapie der Iridocyclitis tuberculosa. Inaug. Dissertation. Tübingen, 1901.

³ Thorner: See section on Treatment.

⁴ Köhler: Loc. cit.

⁵ Brown: Klebs, loc. cit., p. 554.

⁶ Brown: Loc. cit.

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reports that of 200 treated cases three developed nephritis. But two of these had advanced tuberculosis. The slight admixture of phenol is too small to have any deleterious influence. We may say that the only danger of subcutaneous tuberculin used therapeutically is the danger of neglecting the rules that are laid down for its rational employment, as will be explained. When in surface or surgical tuberculosis the tuberculin is applied directly to the lesion, great care should be taken not to evoke more than a very mild focal reaction; otherwise an extension is conceivable.

As regards the conjunctival test, in several thousand instillations we have had but two untoward results, one patient developing phlyctenular conjunctivitis, which subsequently completely healed; the other an episcleritis, which also healed, and which we are not sure was due to the test. It might be objected that after receiving the tests many of our patients never return and that there may have been some accidents of which we had no knowledge. While this possibility must be allowed, we consider it highly improbable. It seems reasonable to presume that had any severe eye symptoms later developed the patients would have returned for observation, and they could not have gone to the eye clinic without being transferred by us. One is, however, obliged to consider with respect the many reports of severe recurring conjunctival inflammations, of phlyctenular conjunctivitis and of corneal ulcers with permanent opacities. Some observers have had such accidents frequently, while others, and notably those who have used the test most, say they have seen no ill effects. It is important that many ophthalmologists take a stand against the test. Why results should be so divergent it is difficult to explain. Most of the unfavorable results have followed instillations in already diseased eyes or of too strong solutions, but this is not true of all the cases. Two of

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Schrumpf's¹ patients developed corneal ulcers after an instillation of 1 per cent. old tuberculin. Both were over sixty years of age. There are certain precautions that must be followed in making the test, and when these are observed accidents will be fewer. For at least the first instillation only a weak solution should be used, not over 1 per cent. old tuberculin, and we should think less than 0.5 per cent. of the precipitated tuberculin, although we have had very limited experience with the latter. The eyes should always be carefully inspected before the instillation is made, and the least abnormality regarded as a contraindication. A second instillation should never be made in the same eye, at least for several years. Considering the tendency of old people to conjunctival inflammation, and particularly to corneal ulceration, it were probably better to exclude these from the test. We think that our experience justifies us in continuing to use the conjunctival test after the method we have outlined and with the precautions indicated. This we have done since these data were compiled, and have never had another untoward result.

A second objection is that a conjunctival instillation, whether there be a reaction or not, often renders subsequent administration of tuberculin subcutaneously for diagnosis or treatment, if not dangerous, at least unpleasant. At times a recurring reaction comes on after the dose given is not large enough to liberate a general reaction. This secondary reaction not only may be more severe than the first, but may be severe even though absent after the instillation. It is said that under tuberculin treatment constant recurrences may make injections very discomforting. Such manifestations during treatment, however, must be very uncommon. In a large num-

¹ Schrumpf: Ueber gefährliche Folgen der Calmetteschen Ophthalmoreaktion. München. med. Wehnschr., 1908, ix, 2225.

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ber of cases we have observed it only twice. It is the diagnostic injections that are particularly influenced, and our tables show to what extent these recurrences follow. In only two instances were the conjunctival inflammations at all severe. If we feel that it is advisable to give subcutaneous injections to obtain a focal reaction, we believe a previous conjunctival instillation need not deter us. In our cases all such recurring reactions have promptly and satisfactorily subsided. It would be better, of course, to omit the conjunctival test in patients to whom we wish to give tuberculin subcutaneously.

Practically the only danger attending the cutaneous or intracutaneous test is that of infection following uncleanness. We ourselves have had no trouble whatever from this direction. Very rare indeed are the reports of a general reaction following a skin or eye test. These reactions, if they have really been such, have been extremely mild.

Should the skin tests be administered within a tuberculous area, a focal reaction might result. Such has been reported. But in this case what has really been given is not a skin test but an intrafocal inoculation.

III

THE USE OF TUBERCULIN IN TREATMENT

Methods of Preparation.—Tuberculin, although in Germany sometimes called lymph, is not at all derived from serum, but is a product of bacterial growth upon a proper culture medium. Tuberculin, in our present state of knowledge, is not a single substance, but a generic name including a large variety of preparations that are known individually as Tuberculin, with some qualifying word or phrase as Old, New, etc. Some of the tuberculins, however, are known by terms less indicative of their real nature, as Tuberculol, Endotin. All tuberculins, whatever their name and however subtle or complicated the process of their manufacture, have this important factor in common: They are all derived from cultures of the tubercle bacillus. The diverse qualities of the numerous tuberculins are obtained by cultivating varying types of the tubercle bacillus, by changing in some way the medium on which the bacillus is to grow, by allowing the growth to continue for varying intervals of time, by using all or only part of the substance present in the culture-tube at a stated time, and, finally, by subjecting the substances used, at some stage of the process of manufacture, to various physical, chemical, electrical or biological influences. For example, the human or the bovine type of the bacillus may be inoculated into the culture-fluid; the culture-fluid may contain liver extract, or may lack peptone; young or old cultures may be used; the intact bacilli may be filtered off, and they themselves or only the filtrate may be used; the substances

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employed may be heated, or subjected to osmosis, or treated by chemical agents, such as acids, alkalies, alcohol, etc., or they may be subjected to electrolysis. Biologically the substances may be modified by allowing organisms other than the tubercle bacillus to grow with it symbiotically. It need hardly be added that, whatever the method of preparation, care is taken that the final product contain no living tubercle bacilli.

The reason for the continued production of more and more tuberculins lies in the supposed advantages of each new product over the older ones, for the purpose of either diagnosis or treatment. However, modernity alone does not confer value on a tuberculin, and the present stage of our knowledge forces us to yield greatest respect to a few, and these not the youngest, of the large group. Indeed, so numerous have the tuberculins become that the great majority must in this volume be unnamed. Of those mentioned a few, because of their intrinsic merits, or because of especial historic interest, will receive more extended notice.

The first tuberculin in point of time is still the first in importance in the diagnosis of tuberculosis; and in treatment, too, it may be regarded as among the most useful, if not the most useful. This tuberculin is known as *Koch's Original Tuberculin* (synonyms: Tuberculin Original, Alt Tuberkulin, Old Tuberculin, Original Tuberculin), and is frequently designated by the symbol O. T. (not to be confounded with T. O.). It is prepared as follows: A bouillon medium enriched with 5 per cent. glycerin and slightly alkaline is inoculated with tubercle bacilli of the human type. In a broad flask this is allowed to incubate at body temperature for six to eight weeks, at the end of which time the bacilli have grown into a flat sheet covering the surface of the fluid. Moistened fragments of the growth may have reached the bottom of the flask or may still be

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suspended at various depths. The entire contents are then subjected to a current of steam over a water-bath for the purpose of sterilization, and for concentration unto one-tenth of the original volume. The glycerin, not evaporating, thus constitutes 50 per cent. of the resulting mixture. At this stage the bacteria (which have now been killed) are removed by filtration through a Chamberland filter. There results a clear, brown fluid, of a characteristic odor, which keeps indefinitely, and is ready for use. This preparation¹ was promulgated on October 22, 1891.² Its use gave rise to the period of "tuberculin delirium" and to the consequent reaction. We shall subsequently discuss the composition of the various tuberculins and tell also what the various makers expected to find in their respective tuberculins; what reasons they assigned for the excellence of any one product, and by what bacteriological principles and accepted aphorisms they were guided. For the present we shall continue to describe briefly the method of manufacture of some of them.

The next tuberculin to be promulgated by Koch (in 1897) is known as T. R., *New Tuberculin*, or *Tuberculin Residue*.³ It is prepared by growing, as for O. T., highly virulent cultures, as young as possible. After four to six

¹ R. Koch: Ueber bakteriologische Forschung. Centralbl. f. Bakteriolog., 1890, viii, 563.

Weitere Mittheilungen über ein Heilmittel gegen Tuberkulose. Ibid., 673.

Weitere Mittheilung über das Tuberkulin. Deutsch. med. Wehnschr., 1891, xvii, 101 and 1189.

² On Nov. 18, 1890, Koch alluded to a "remedy" without describing the mode of preparation. On Jan. 15, 1891, he describes the remedy as "a glycerin extract of pure culture of the tubercle bacillus." It was not until Oct. 22, 1891, that the description of the manufacture of O. T. from fluid cultures was published. His delay in announcing the exact mode of preparation was due to his desire not to hamper the originality of other workers in devising varieties of the product. One wonders whether the resulting crop pleased or displeased the master.

³ R. Koch: Ueber neue Tuberkulinpräparate. Deutsch. med. Wehnschr., 1897, xxiii, 209.

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weeks the bacilli are filtered off and dried in a vacuum. One gram of the dried tubercle bacilli is ground in an agate mortar until a sample shows no intact bacilli. To the pulverized mass there is added 100 c. c. of distilled water, and the mixture is then centrifugalized. The clear fluid resulting from this first centrifugalization is poured off and is known as Tuberkulin Oberes (T. O.). It contains substances not precipitable by glycerin. The sediment deposited by centrifugalization is again dried, powdered, and again taken up by a small quantity of water. Centrifugalization is repeated, and the previous cycle again gone through, until there is no sediment except that composed of gross, accidental particles. The fluids resulting from all of the centrifugalizations, except the very first, are united and should total not more than 100 c. c. This fluid is slightly opalescent and is precipitable by 50 per cent. glycerin. To the opalescent fluid 20 per cent. glycerin is added for preservation. The resulting suspension is known as T. R., and it should contain in each cubic centimeter 2 milligrams of solids, representing 10 milligrams of dried tubercle bacilli.¹ From the mode of manufacture it was assumed that T. R. contains none of the secretions of the bacilli as does O. T., and that it does contain substances from the body of the bacilli, which O. T. speciously does not contain.

A still later tuberculin made by Koch (1901) is known as *Bazillen-Emulsion*, or B. E.² This, as the name indicates, is an emulsion of tubercle bacilli. The culture is grown as for O. T. The bacilli are filtered off, ground but not washed. One part of the pulverized material is emulsified in 100 parts of distilled water, and an equal volume

¹ W. G. Ruppel: Die Herstellung des neuen Tuberkulins (Tuberkulin T. R.). Deutsch. med. Wehnschr., 1908, xxxiv, 185.

² R. Koch: Ueber die Agglutination der Tuberkelbazillen und über die Verwerthung dieser Agglutination. Deutsch. med. Wehnschr., xxvii, 1901, 829.

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of glycerin added, making 50 per cent. glycerin emulsion, one cubic centimeter of which contains the immunizing substances of 5 mg. of dried tubercle bacilli. B. E. was assumed to contain the entire contents of the bodies of the tubercle bacilli without any of the soluble excretions into the culture medium. Not having been washed as T. R. has been, it is also assumed to retain the extractives lost in the preparation of the former. Note that all the products of Koch, with the exception of O. T., are unchanged by heat, the bacilli in the others being killed mechanically.

While Koch was elaborating these various tuberculins others busied themselves to the same purpose. In 1905 Denys, a Belgian, announced his *Bouillon Filtrate*, or B. F. (Le Bouillon Filtré),¹ which has held its own against other varieties, and is to-day widely used in the treatment of tuberculosis. The culture is prepared as for making Original Tuberculin (O. T.). At the end of the required interval, however, the mixture is not heated or concentrated in any way, but is at once passed through a bacteria-proof porcelain filter. The residue is rejected. The filtrate, a clear fluid, is supposed to contain only the soluble secretions of the bacilli, plus the metabolized culture medium, and without any further modification is ready for use.

In 1903 Béraneck announced a tuberculin for which he claims only minimal toxicity and a high content of specific substances. He cultivates the bacilli on a non-peptonized 5-per-cent. glycerin bouillon medium, which is not neutralized. The filtrate from this culture is known as T. B., or toxin-bouillon. The residue is shaken for a long time at 60°-70° C. with 1-per-cent. ortho-phosphoric acid. Equal volumes of the unheated toxin-bouillon and of the ortho-phosphoric acid extract of the bacillary bodies are united

¹ Denys: Le bouillon filtré. Paris, 1905.

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to form *Béraneck's tuberculin*, of a concentration known as H.¹

A tuberculin that has been widely used in the United States is known as *von Ruck's Watery Extract*.² It is prepared as follows: Concentrate a culture in vacuo at 55° C. to 1-10 volume. (This takes about a month.) Filter through paper, then through porcelain. Precipitate with an acid solution of sodic-iodid of bismuth. Filter and neutralize the acid solution. Filter again. Precipitate with absolute alcohol to make 90 per cent. alcohol, and filter. Wash the precipitate with absolute alcohol. Dry the precipitate and make a 1-per-cent. aqueous solution. Filter. The last filtrate is v. Ruck's tuberculin.

In order to understand the efforts of the seekers after an ideal tuberculin, it is well to view for a moment that experiment which eventually led Koch to create the first of the numerous tuberculins.³ If an emulsion of living tubercle bacilli is inoculated into a cutaneous wound of a healthy guinea pig, the wound closes, and in the first few days seems to have healed. But in about ten to fourteen days a hard node forms which ulcerates, and remains ulcerated until the death of the animal from a generalized tuberculous infection. Concurrently there is marked involvement of the lymphatic apparatus draining the ulcerated

¹ Béraneck: Une nouvelle Tuberculine. Cong. Internat. de la tuberculose. Paris, 1905, i, 857.

Le traitement de la tuberculose par les tuberculines, et plus spéc. par la tub. Béraneck. VI Internat. Tuberculosis Congress. Washington, 1908, i, Pt. 2, 725.

Sahli: Tuberkulinbehandlung und Tuberkuloseimmunität. Basel, 1910.

² v. Ruck: Erfahrungen mit Tuberkulin und mit anderen Produkten des Tuberkelbazillus in der Behandlung der Lungenschwindsucht. Ztschr. f. Tuberk., 1907, xi, 493.

Ueber die spezifische Behandlung der Lungentuberkulose. Ibid., 1910, xv, 443.

³ R. Koch: Weitere Mittheilung über das Tuberkulin. Deutsch. med. Wehnschr., 1891, xvii, 101.

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area. However, if the subcutaneous inoculation occurs in a guinea pig which already harbors a generalized infection with the tubercle bacillus (due to an inoculation four to six weeks previously), the animal, within two or three days, becomes acutely sick. Simultaneously the wound, which has closed, just as in the uninfected animal, becomes hard and dark even to a radius of 1 cm., without, however, forming a definite nodule. In the next few days it is apparent that the dark skin is necrotic, and is being sloughed off. There results a flat ulceration which heals rapidly and permanently. The neighboring lymph glands, strange to say, are not involved; and the guinea pig lives longer than a tuberculous guinea pig not so inoculated.

The essential results, then, of a reinoculation of an already tuberculous guinea pig are: first, a prolongation of life; second, an acute general and local reaction. Koch hoped to obtain the beneficial results of such a reinoculation also in human beings, but without the disagreeable local necrosis and sloughing. If the necrosis were caused by some component of the bacilli not needed for eliciting the favorable general reaction, his hopes might be realized. This thought—that the tubercle bacilli and their secretions *in vitro* contain substances both desirable and undesirable for the purpose of treating human beings—is what has animated all makers of new tuberculins. And their methods of procedure have been dominated by what they considered desirable or undesirable in the composition of the bacillus and its secretions, and in that of the culture-medium.

Koch had reason to believe that the healing action of the inoculated bacilli is due to something they secrete, and this secretion he believed to be present in his Old Tuberculin. At any rate, by injecting Old Tuberculin subcutaneously into tuberculous guinea pigs, he produced the rapid general reaction before spoken of, without any local

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necrosis or sloughing. But Old Tuberculin, similarly injected into a healthy guinea pig, produced no reaction whatever, either local or general. The general results produced by O. T. being so analogous to those obtained in his first (vaccine) experiment, and proceeding, moreover, without local necrosis, Koch then promulgated his Old Tuberculin as a specific cure for tuberculosis in human beings.

The supposed composition of Old Tuberculin was influenced by the then extant theories concerning soluble and insoluble toxins of bacteria. The soluble toxins (or exotoxins) were said to be elaborated in the body or in the culture-medium, or wherever the bacillus happened to grow; and, being soluble, they were, of course, to be found free in the culture-fluid. The insoluble toxins (or endotoxins) were thought to be present in the bacillus itself, and could be liberated only by the death and destruction of the latter. Koch considered the exotoxins of the tubercle bacillus to be present in O. T. The endotoxins he held responsible for the local necrosis and sloughing in the above-described experiment, and considered them absent from O. T. The exotoxins were, of course, thought to be responsible for the constitutional reaction. It nowhere appears that Koch thought the specific substance or substances dissolved in the culture-fluid to have been materially altered by the heat applied in the process of preparing O. T. It was, too, an open question with Koch as to whether the exotoxin, or endotoxin, was single or multiple.

Under the influence of theories of immunity, it came to be held that the explanation of at least a part of the action of tuberculin is the stimulation of the cells to the production of antibodies to the toxin or toxins contained in the injected tuberculin. But since it was accepted that bacteriolytic substances would be formed only after the injec-

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tion of intact or fragmented tubercle bacilli—with their contained endotoxins—Koch added T. R. to his armamentarium, and later still B. E. in order to make the production of anti-bacterial substances still more complete. Furthermore, to obtain as varied as possible a supply of antibodies, the use of several tuberculins (as O. T. with B. E.) for the same patient was recommended.

As was pointed out in the First Section (page 9), the action of tuberculin is specific, it having no toxic effect on healthy animals. Such toxic effects in healthy animals as may be produced by the use of huge quantities of tuberculin were commonly attributed to by-products in the culture-medium, or to removable, undesirable components of the bacillary substance itself. The ideal tuberculin, then, would be one containing the specific element or elements with none of the substances in themselves toxic to non-infected animals. The specific element or elements of tuberculin, the supposed essential, specific secretion of the tubercle bacillus, has, however, not yet been chemically or biologically isolated or identified. It is, therefore, important, argued many (among them Denys), to interfere as little as possible with the product of the growth of the tubercle bacillus in vitro, since any modification to which it may be subjected may, for all we know, weaken its specific potency, and even aid in producing the undesirable, non-specific, toxic substance. In accord with these views, Denys produced his Bouillon Filtrate, which, it will be remembered, unlike Old Tuberculin, has not been subjected to heat. Although not concentrated, and, therefore, in any volume representing only one-tenth the volume of O. T., yet it produces the phenomena of sensitiveness, in many patients, by the use of a smaller dose than of O. T. This fact justifies, apparently, the assertion that the heat applied in the preparation of O. T. has, in some way, weakened it. It is also asserted that to non-infected animals

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B. F. is less toxic than an equivalent volume of O. T. Denys did not believe that anything other than the soluble components of the culture were needed for treatment, and did not make any bacillary extracts.

It should be stated here that the controversy as to the greater potency of B. F. or O. T. cannot be so easily adjudicated as might appear from the above facts. For a patient immunized to a large dose of B. F. very often cannot take an equivalent dose of O. T. without signs of a reaction. Whether these signs are due to specific substances in the O. T. elaborated from the bacillary bodies by the heat, or whether they are due to toxic substances formed at that time, remains to be seen.

Béraneck claims for his tuberculin a still greater specificity and a still lower toxicity than for B. F. It will be remembered that his tuberculin contains also extracts of the bodies of the tubercle bacilli. Sahli,¹ on the basis of clinical experience and theoretical data, believes it to be the most efficient of the tuberculins.

Enough has been said to explain the efforts of other inventors of new tuberculins. The aim is always to get the specific substances with as little as possible of any toxic substances. Especially since the vogue of ideas concerning anaphylaxis has the effort been made to rid the entire culture product of any substances that might cause anaphylactic disturbances apart from the specific sensitizing action. Thus tuberculocidin and tuberculol are examples of attempts at isolating the pure principle; and Endotin or Moeller's Tuberculin is an example of the endeavor to get rid of protein-substances in the culture-fluid itself. v. Behring's work has proceeded rather on the line of vaccines, the impelling idea being that of losing none of the immunizing bodies. Rosenbach proceeds upon an entirely new idea of modifying the tuberculin by a symbiotic process.

¹Sahli: Loc. cit.

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We have now spoken in a rather general way of the composition of tuberculins, because our aim has been rather to indicate the forces by which the workers were impelled than to disclose our actual knowledge and ignorance. We now proceed to a presentation of the present-day knowledge of the composition of the various tuberculins, and to a critique of those tuberculins and of tuberculin in general.

The mode of manufacture of those few tuberculins which are most extensively used has already been described. There remain many others which, while not meeting with the same approval of clinicians, are yet of interest as illustrating the groping toward truth. As many of these resemble each other closely, and indeed resemble those already described, it is timely to present a grouping which will help the reader to remember them in a general way. Five groups may be arranged.

Group I consists of the tubercle bacilli themselves, dead or alive, subjected to only slight physical changes. (These are really vaccines.) This group contains B. E., Behring's Vaccines, Tebean, Tuberculo-Sero-Vaccine.

Group II contains tuberculins made by extracting tubercle bacilli without any attempt whatever at the isolation of ultimate principles. In this group are T. R., Béraneck's tuberculin; von Ruck's; the tuberculins derived from the fatty substance of the bacilli; Krehl and Matthes' preparations; Vasilescu's Oxytuberculin; Sciallero's; Maréchal's; Jakob's; Benario's; Cantani's; Turmann's; Rosenbach's; Tuberculo-plasmin; frozen bacilli; Tebesapin, or Prosperol; Tb-L; Ishigami's.

Group III contains preparations derived from the culture-fluids, such as O. T.; B. F.; Jochmann's tuberculin; Iron-tuberculin; Tuberculin purum, or Endotin; Jessen's; Leber and Steinharter's. Some of these belong also in Group II.

Group IV includes modifications which aim at the iso-

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lation of a pure principle. While the members of this group might be placed in one of the other groups, it is meant to indicate that there has been a striving at a far-reaching analysis, with chemical purity as an ideal goal. Here included are Tuberculol, Tuberculocidin; Haentjen's Filtrase; Tuberculo-Nastin.

Group V consists of tuberculins which, as far as the methods of preparation go, might be included in one of the previous groups, but which deserve a distinct grouping, since there is emphasis upon the type of the bacillus to be grown. This type differs in some way from the ones ordinarily employed. Here are Spengler's tuberculins; the tuberculins made from avian or other acid-fast bacilli; Calmette's Cl; autogenous tuberculins.

Description of Group I: Koch's Bacillary Emulsion (B. E.), the most widely used member of this group, has already been described. Two of v. Behring's¹ preparations may be included here—Tulaselaktin and tuberkulase. The latter is a preparation of tubercle bacilli killed by chloral hydrate. Tulaselaktin is a similar preparation which has been saponified into a milk-like suspension by alkalies. Both of these preparations have been withdrawn from the market, and at no time has the mode of manufacture been published.

Tebean (Levy). Virulent human bacilli are shaken in 25-per-cent. galactose at 37° C. for 4½ days, and are then concentrated in vacuo until 1 gram contains 5 mg. of the bacilli, which have now been killed by the concentrated sugar.²

¹ v. Behring: La thérapie immunisante à Marbourg contre la tuberculose. Tuberculosis, 1906, v, 342.

² Levy u. Krenker: Ueber die Wirkung und therapeutische Verwertung der durch Galaktose abgetöteten Tuberkelbacillen. Ztschr. f. Immunität u. exper. Ther., 1909, iv, 286, 292.

Steffen: Ueber die Behandlung der Lungentuberkulose mit Tebean. München. med. Wehnschr., 1910, lvii, 838.

Schrumpf: Ueber die durch abgetötete Tuberkelbacillen beim Menschen

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Tuberculo-Sero-Vaccine of Meyer-Ruppel. In order to obviate local infiltrations caused by B. E., Meyer and Ruppel mix the bacilli with serum of horses immunized against the tubercle bacillus.¹

Group II: Of this group, the principal members, T. R., Béraneck's tuberculin, and von Ruck's Watery Extract, have already been described. Others are:

The Aliphatic Tuberculins: This group is based on the belief that the essential constituents of the tubercle bacillus are aliphatic bodies and can be removed by appropriate agents. Lowenstein² used the extracts obtained by alcohol, alkalies, xylol, alcohol and ether, but found them of no value.

Beck³ made similar preparations with like results. Aronson,⁴ in 1898, in agreement with v. Behring, found that the fatty substances are not completely extracted by the methods till then used. He recommends trichlorethylene, which, in the proportion of 100 c. c. to 3 g. of well-rubbed tubercle bacilli, is to be shaken for two days at

und beim Tiere hervorgerufene "Pseudo-tuberkulose." Centralbl. f. Bakteriöl., Abt. I, 1910, liv, 216.

Hawthorn: Le Bacille de Koch en Émulsion dans la Glycerine. Compt. rend. soc. de biol., 1909, i, 364.

¹ Meyer: Ueber sensibilisierte Tuberkelbacillen-Emulsion (Tuberkulose-Sero-Vaccin). Berl. klin. Wehnschr., 1910, xlvii, 926.

Citron: Kritisches und Experimentelles zur Tuberkulin-therapie. Berl. klin. Wehnschr., 1909, xlvi, 2288.

Rolly: Zur spezifischen Diagnostik und Therapie der Lungentuberkulose. München. med. Wehnschr., 1910, lvii, 833.

Wolff-Eisner: Ueber entgiftete Tuberkuline. I. Sensibilisiertes Tuberkulin. Berl. klin. Wehnschr., 1910, xlvii, 2147.

² Lowenstein: Über Tuberkulinpräparate zu diagnostischen und Heilzwecken, p. 369. In Kraus u. Levaditi: Handbuch der Technik und Methodik der Immunitätsforschung. Erster Ergänzungsband. Jena, 1911, 355. (This article contains much information also about other tuberculins.)

³ Beck: Beiträge zur Immunitätsfrage bei der Tuberkulose. Ztschr. f. exper. Path. u. Therap., 1909, vi, 695.

⁴ Aronson: Zur Biologie der Tuberkelbacillen. Berl. klin. Wehnschr., 1910, xlvii, 1617.

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37° C. The bacilli thus treated lose completely their acid-fast properties. Immunizing experiments with the fatty substances obtained by this extraction are in progress.

Krehl and Matthes¹ shake the tubercle bacilli with 1-per-cent. orthophosphoric acid at 70° C. for six hours. The extract thus obtained is added to an Old Tuberculin which has been still further concentrated. Nothing is known of the action of this tuberculin.

Vasilescu² distills two to three months old glycerin bouillon cultures, and obtains a tuberculin which is toxic even to healthy animals.

Oxytuberculin is prepared by Hirschfelder³ through the agency of hydrogen peroxid. He argues for its efficacy that laparotomy has a beneficial effect on tuberculous peritonitis.

Sciallero recommends an oleic acid extract of tubercle bacilli.

Maréchal's tuberculin is very much like a mixture of T. R. and O. T.

Jakob's tuberculin is vacuum tuberculin containing creosote.

Benario suggested to the Höchst factory that it grow tubercle bacilli on an arsenic medium, since he had good results by combining tuberculin treatment with arsenic given hypodermically. Tuberculins have been made, in

¹ Krehl u. Matthes: Ueber febrile Albumosurie. Deutsch. Arch. f. klin. Med., 1895, liv, 501.

Ibid.: Ueber die Wirkungsweise einiger aromatischer Amide und ihre Beeinflussung durch Einführung der Methyl-oder Aethylgruppe. Arch. f. exper. Path. u. Pharmakol., 1895, xxxvi, 451.

² Vasilescu: Destillotuberkulin. Centralbl. f. Bakteriöl., Abt. I, 1910, liii, 335.

³ Hirschfelder: Die Behandlung der Tuberkulose und anderer infectiösen Krankheiten mit Oxytoxinen. Deutsch. med. Wehnschr., 1897, xxiii, 25 (Therap. Beilage).

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pursuance with his suggestion, from tubercle bacilli containing 3-per-cent. arsenic as an intimate part of them.

Cantani¹ uses an iodine-protein combination of the tubercle bacillus. He claims by this to avoid the febrile effects of ordinary tuberculin. Turmann² has made a similar iodine preparation.

Rosenbach³ modifies the tubercle bacillus by symbiosis. In order to effect the change, he plants, in a six-to-eight-week culture of the tubercle bacillus, the fungus *trichophyton holosericum album*, and incubates for ten to twelve days at 20°-22° C., at the end of which interval the mass of tubercle bacilli is completely interwoven with the hyphæ of the fungus. The mass is then lifted from the culture-fluid, mixed with a glycerin-phenol solution, rubbed, filtered, and added to the filtered culture-fluid. The volume is made to be exactly one-tenth of the original Tb + Tr mass, and 1/2-per-cent. phenol added for preservation. The bacilli that have been submitted to such a symbiotic influence stain darker than normal bacilli, and present involution forms. The fungus is said to destroy the toxic and not the immunizing power of the tubercle bacillus.

Buchner and Hahn⁴ tried to imitate Buchner's extraction of the active principle of yeast-cells. They grind tubercle bacilli with quartz sand, and then subject the mixture to the action of the Buchner press. The expressed juice is a preparation analogous to T. R.

¹ Cantani: Ueber die antitoxische Wirkung des Jods bei Tuberkulose. *Ztschr. f. Hyg. u. Infektionskrankh.*, 1909, lxiii, 34.

² Turmann: Ueber die Behandlung der Tuberkulose mit einem spezifisch wirkenden Jodpräparat. *München. med. Wehnschr.*, 1909, lvi, 1532.

³ Rosenbach: Ein neues Tuberkulin. *Deutsch. med. Wehnschr.*, 1910, xxxvi, 1513.

⁴ Buchner: Gewinnung von plasmatischen Zellsäften niederer Pilze. *München. med. Wehnschr.*, 1897, xlv, 1343.

Hahn: Immunisirungs-und Heilversuche mit der plasmatischen Zellsäften von Bakterien. *München. med. Wehnschr.*, 1897, xlv, 1344.

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MacFadyean and Rowland used fragmented frozen bacilli as a tuberculin.

Tebesapin or Prosperol, made by Zeuner¹ of Berlin, is a tuberculin composed of substances extracted from the tubercle bacilli by means of sodium oleate. The substances are said to be fat, wax and proteid. The sodium oleate is considered by Zeuner to be an excellent substance for dissolving the capsule of the bacillus. His tuberculin is made as follows: Tubercle bacilli are shaken for four days at 37° C. with an emulsion of sodium oleate in water (1 to 60). Then heat at 70° C. to 72° C. for one hour, after which continue to shake for three days at 37° C. Centrifugalize, filter, and dilute the filtrate at 1:100. Add 4-per-cent. tricoresol, and Tebesapin is the result.

Deycke and Much² split the tubercle bacilli into fatty and proteid components by means of lecithin. They have reason to think that the bacteriolytic agent is not the lecithin itself, but a yet unknown body associated with the lecithin. Hence lecithins derived from various sources differ in their bacteriolytic power. A tuberculin known as Tb-L is made by them, for which lecithin prepared from brain and egg is the splitting substance.

A later tuberculin³ has been made by the same authors, for which they use cholin and neurin as the bacteriolytic forces. One gram of tubercle bacilli is partially split in three hours at 37° C. by ten grams of neurin, and completely so at 56° C.

Ishigami⁴ destroys the capsule by subjecting dried

¹ Zeuner: Neue Ziele der spezifischen Tuberkulosebekämpfung. Ztschr. f. Tuberk., 1909, xv, 135.

² Deycke u. Much: Untersuchungen über endobazilläre Eiweisskörper. Med. Klin., 1908, xl, 1541.

³ Deycke u. Much: Bakteriolyse von Tuberkelbazillen. München. med. Wehnschr., 1909, lvi, 1985.

⁴ Ishigami: Tuberculo-toxoidin and immunization serum. VI Internat. Cong. on Tuberculosis. Washington, 1908, i, pt. 1, 248.

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tubercle bacilli to strong sulphuric acid. Then water is added in the proportion of 10 to 1. The fats float to the surface, and the sediment, after being filtered off, is dissolved in weak alkali. The resulting substance is known as tuberculo-toxoidin, and is recommended as a tuberculin.

The principal members of *Group III* (tuberculins from culture-fluids) have already been described. These are, it will be recalled, Koch's O. T. and Denys' B. F. Only a few more need mention.

Jochmann,¹ working under the direction of Koch, attempted to meet the arguments of those who attributed much of the effect of O. T. to the albumoses of the culture-medium. Following the lead of Proskauer, Beck² and Fraenkel,³ he grew the bacilli on a protein-free medium made of water, 1,000; asparagin, 8; ammonium lactate, 6; sodium chlorid, 5; glycerin, 40; neutral sodium phosphate, 2. From this culture-fluid Jochmann prepares tuberculins which he deems less toxic but therapeutically not more efficient than those tuberculins derived from the usual medium.⁴ One of these is known as Tuberculin A. F. (=albumose-free). The other is called Tuberkulin Hell (=clear tuberculin). A. F., unlike O. T., is heated only to 37° C., and is concentrated to only 25 per cent. of the original volume. Tuberkulin Hell is heated to 100° C. Jochmann's clinical work was done largely with A. F.

Iron-tuberculin is prepared from O. T. according to the following method of Ditthorn and Schultz: Dilute 10 c. c.

¹ Jochmann: Kongr. f. innere Medizin, 1910.

Jochmann and Möllers: Ueber die Behandlung der Tuberkulose mit dem Kochschen albumose-freien Tuberkulin. Deutsch. med. Wchnschr., 1911, xxxvii, 1297.

² Proskauer u. Beck; Beiträge zur Ernährungs-physiologie des Tuberkelbacillus. Ztschr. f. Hyg. u. Infektionskrankh., 1894, xviii, 128.

³ Fraenkel: Hyg. Rundschau, 1894.

⁴ Freymuth: Erfahrungen mit eiweissfreiem Tuberkulin. Beitr. z. Klin. d. Tuberk., 1911, xx, 215.

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of O. T. with five times its volume of water. Precipitate with a 12-per-cent. solution of iron-oxychlorid to excess. Filter. Wash the precipitate and dissolve in 1-per-cent. NaOH. Then add 25-per-cent. glycerin to make a volume of 40 c. c. Analogous tuberculins have been made also from the bacillary mass itself. The therapeutic experiments show no essential difference between the action of the iron-tuberculins and the ordinary varieties.¹

Gabrilowitsch maintains² that, by treating a product similar to O. T. with alcohol, xylol, ether and chloroform (in a manner not definitely stated), he thereby gets rid of undesirable fats, carbohydrates and proteins. The resulting tuberculin is called Tuberculinum Purum, or Endotin, and is claimed to be free from albumoses.

Armand-Delille³ claimed that the ether extract of the tubercle bacillus promotes caseation and that the chloroform extract promotes sclerosis. Jessen⁴ therefore uses a bouillon culture-fluid from which the ether and chloroform soluble components have been extracted. The bacillary bodies are not used.

Leber and Steinharter⁵ prepare a similar tuberculin by

¹ Ditthorn u. Schultz: Ztschr. f. Immunit., 1909, ii, 5.

Ohm: Med. Klin., 1909, No. 4.

Schultz: Klinische Erfahrungen mit Eisentuberkulin. Berl. klin. Wehnschr., 1909, xlv, 1721.

² Gabrilowitsch: Ueber das Endotin, die wirksame Substanz des Kochschen Alttuberkulins. Tuberculosis, 1909, viii, 507.

Gordon: Ueber das Endotin, die isolierte spezifische Substanz des A. T. (Koch). Deutsch. med. Wehnschr., 1910, xxxvi, 1746.

Camphausen: Einige Mitteilungen über die Behandlung mit Endotin (Tuberkulin pur.). Beitr. z. Klin. d. Tuberk., 1911, xx, 247.

Wolff-Eisner: Ueber entgiftete Tuberkuline. II. Das Endotin. Berl. klin. Wehnschr., 1910, xlvii, 2200.

³ Armand-Delille: Arch. Experimentales, 1902.

⁴ Jessen: Zur Verbesserung der Tuberkulinbehandlung. München. med. Wehnschr., 1908, lv, 1776.

⁵ Leber u. Steinharter: Diagnostische Impfungsversuche mit einem fettfreien Tuberkulin. München. med. Wehnschr., 1908, lv, 1324.

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shaking equal parts of chloroform and O. T. for six hours.

Group IV, now to be described, contains tuberculins whose makers had in mind, more or less, the isolation of a definite active principle, or of several such. While the members of this group, as far as regards their composition, might have been distributed among the remaining groups, we have united them here, as a mark of respect for the evident strivings of their authors at a strict isolation of the desirable components from their undesirable accompaniments.

Perhaps the most famous is Landmann's¹ Tuberculol. Landmann believed that in the process of heating O. T. to 100° C. substances are destroyed that at lower temperatures can be extracted. In order to obtain not only those extractives that cannot withstand heating, but also those that cannot be extracted without heat, he uses fractional extraction at various temperatures. He grows in bouillon a highly virulent strain of the human type of the tubercle bacillus. The bacilli are filtered off by filter-paper, fragmented, and the fatty components removed. Extraction at 40° C. then occurs by a glycerin-normal salt solution. After decantation, the residue is again extracted at 50° C. and so on up to 100° C. The united extracts are now concentrated in vacuo at 37° C. In order to make the aggregation of tuberculous toxins still more complete, the concentrated culture-fluid is now added to the combined extractives; and the entire amount is filtered through porcelain for sterilization. Finally, ½-per-cent. phenol is added. The product is marketed by Merck as Tuberculol A. Tuberculol B is the bacillary extract, Tuberculol C the bouillon component. D, E, F are the corresponding preparations made from the bovine type of the bacillus, and are known as

¹ Landmann: Ueber eine neue Methode der Tuberkulose-Toxin-Behandlung. Centralbl. f. Bakteriol., Abt. I, 1900, xxvii, 871.

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Bovotuberculol. The essential property of tuberculol, as contrasted with O. T., is its enormous toxicity to healthy guinea pigs.

Tuberculoctidin represents the attempts of Klebs¹ to purify tuberculin by alcohol and bismuth precipitation. Antiphthisin is made from the culture-fluid, by precipitating with acetic acid and then with alcohol containing sodium-bismuth-iodid. He also produced tuberculo-protein and tuberculo-sozin; the latter being a glycerin extract of dead tubercle bacilli.

Haentjens' Filtrase. Haentjens² attempts to obtain the normal secretions of the tubercle bacilli by growing them in permeable capsules. The toxins which diffuse through the walls of the capsule are thought by him to be very much like those secreted by the bacilli in the human body. Tubercle bacilli grown three to five weeks on glycerin potato or on Hess's medium are placed in the filters with an equal quantity of NaCl powder. The capsule is placed in distilled water, so that after the exchange of water and salts a normal salt solution is produced. In this the bacilli continue to live and are supposed to secrete toxins at 37° C. during their 14 to 30 days' stay in the incubator. The toxins are diffused into the water, thus form-

¹ Klebs: Ueber die Wirkung des Kochschen Mittels auf Tuberkulose der Thiere, nebst Vorschlägen zur Herstellung eines unschädlichen Tuberkulins. Wien. med. Wehnschr., 1891, xli, 632.

Ueber heilende und immunisierende Substanzen aus Tuberkelbacillen-Kulturen. Centralbl. f. Bakteriöl., Abt. i, 1896, xx, 488.

Ueber Entstehung und Behandlung der menschlichen Lungentuberkulose. Deutsch. med. Wehnschr., 1907, xxxiii, 577.

Immunisation bei Tuberkulose. Deutsch. med. Wehnschr., 1908, xxxiv, 97.

² Haentjens: Die Ursachen der relativen angeborenen Immunität des Hundes gegen Tuberkelbazillen (Tuberkeltoxin-Studium). Ztschr. f. Tuberk., 1907, xi, 230.

Tuberkeltoxin-Studium. II. Ztschr. f. Tuberk., 1907, xi, 323.

Die Behandlung mit Filtrase, einem neuen Mittel gegen Tuberkulose, und die damit erzielten Resultate. Tuberculosis, 1909, viii, 239.

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ing the Filtrase. Animal experiments show a thermal but no lethal effect with this tuberculin.

Nastin, and tuberculo-nastin.¹ Nastin is a crystallizable, neutral glycerin fat extracted from *Streptothrix leproides*, an organism closely related to the leprosy bacillus, and isolated in pure culture from a case of leprosy by Deycke and Reschad Bey. This fat seems to be the active agent of *S. leproides*, and, with it, immunizing work was carried on both against the leprosy and the tubercle bacillus, on the assumption that the fats of all those organisms are closely allied.

Later Deycke succeeded in obtaining from the tubercle bacillus a neutral fat, tuberculo-nastin, which seems to be identical with nastin and common to many acid-fast bacilli. Nastin, or tuberculo-nastin, is claimed by Deycke and Much to be an excellent immunizing agent against the tubercle bacillus, especially if the nastin be combined with Benzoylchlorid (or Ketyn). The combination is known as Nastin-B.

Group V is differentiated from the other groups by the use of other than the usual (human) type of the tubercle bacillus for the preparation of the tuberculin. The most noted tuberculins of this group are Spengler's.² Spengler, seizing upon the statement made by Koch in 1901 at the International Congress on Tuberculosis as to the existence

¹ Deycke u. Bey: Neue Gesichtspunkte in der Leprafrage. Deutsch. med. Wehnschr., 1905, xxxi, 489, 545.

Ein bakterielles Fett als immunisierende Substanz bei der Lepra, seine theoretische Bedeutung und seine praktische Verwendung. Deutsch. med. Wehnschr., 1907, xxxiii, 89.

Much: Nastin, ein reaktiver Fettkörper, im Lichte der Immunitätswissenschaft. München. med. Wehnschr., 1909, lvi, 1825.

² C. Spengler: Ein neues immunisierendes Heilverfahren der Lungenschwindsucht mit Perlsuchttuberculin. Deutsch. med. Wehnschr., 1905, xxxi, 1228, 1353; *ibid.*, 1904, xxx, 1129.

Neue Färbenmethoden für Perlsucht- und Tuberkelbacillen und deren differential Diagnose. Deutsch. med. Wehnschr., 1907, xxxiii, 337.

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of two types of the tubercle bacillus—a bovine and a human—arrived at the conclusion that the secretions, too, of these types differed from each other. Reasoning from the success of Jenner in immunizing against small-pox by the use of a virus similar to, but not identical with the virus producing the disease, he was the first to maintain the value of bovine tuberculins in immunizing against the human type. This process Spengler called “Gift-Jennerisation,” and he regarded the bovine toxins as being the weaker, at least for human beings.

The following tuberculins have been manufactured by Spengler:

1. A T O = Old-Original Tuberculin, a preparation from the human type, corresponding to B. F. (Denys).

2. P T O = The analogous preparation from the bovine type (P = *Perlsucht* bacillus—the German for bovine bacillus).

3. Vacuum Tuberculin = A T O concentrated in vacuo at room temperature to 1-10 volume.

4. Bovine-Vacuum Tuberculin is a similarly concentrated P T O. Preparations 3 and 4 differ from Koch's O. T. in being concentrated at a lower temperature.

5. T B E = A human bacillary emulsion similar to Koch's preparation.

6. P E = A preparation analogous to T B E, derived from the bovine type of the bacillus.

Spengler has also made two vaccines: T B V, from the human type, and P V, from the bovine type. The process of manufacture of the vaccines he has not published.

Many workers, pursuing still further the idea of procuring immunity against the human type by the process of Jennerization suggested by Spengler, have prepared tuberculins from still other acid-fast bacilli than the human and bovine tubercle bacillus.

Roux prepared a tuberculin from the avian type of the

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bacillus. The piscian type was used by Terre, Dubard and Romant, and Ravant. Möller¹ used the blindworm tubercle bacillus, and also the Grass I and Grass II bacilli. *Bacillus tuberculoides* I was used by Beck, the butterbacillus by Babes, the pseudo-bovine bacillus of Möller by Zupnik.² The last-named author used also various streptothrices. Feistmantel,³ too, employed an acid-fast streptothrix. Of all these tuberculins, Feistmantel's is the only one that is more toxic to tuberculous animals than tuberculin from the human type. Some of these living acid-fast bacilli have also been used as vaccines, but neither they nor their tuberculins have yielded any encouraging results.

Calmette's Cl: Calmette⁴ has made a tuberculin from the bovine type of the tubercle bacillus, which he designates as Cl, and for which he posits unusually good effects. Heat is avoided, and the statement is made that this tuberculin contains all of the soluble and insoluble toxins of the tubercle bacillus. It is prepared as follows: From a bovine culture grown on the usual glycerin medium the bacilli are removed by centrifugalization. The clear fluid is concentrated in vacuo, and is in vacuo extracted with glycerin. It is filtered and the filtrate is precipitated with alcohol. The last precipitate is dialyzed with ether until free from peptones and salts. The solution is then precipitated by alcohol and dried. The resultant is soluble in normal salt solution and is used for treatment. It seems to be more toxic to animals than Koch's O. T.

¹ A. Möller. Ueber aktive Immunisierung gegen Tuberkulose. Ztschr. f. Tuberk., 1904, v, 206.

² Zupnik: Ueber die Tuberkulinreaktion. Arch. f. klin. Med., 1903, lxxvi, 290.

³ Feistmantel: Säure- und Alkoholfestigkeit der Streptothrix farcinica und die Beziehungen der Streptothricheeen zu den säurefesten Pilzen. Centralbl. f. Bakteriologie, Abt. I, 1902, xxxi, 433.

⁴ Calmette: Les tuberculins et la mesure de leur activité. VI International Congress on Tuberculosis. Washington, 1908, i, pt. 1, 216.

Autogenous tuberculins: There is considerable evidence for the fact that not all the acid-fast bacilli found in sputum are of equal virulence. Assuming that the immunity in tuberculosis is extremely specific in the sense that there are discoverable differences in the immunity reactions with bacilli isolated from different patients, it would be theoretically better to use for each patient a tuberculin made from his own bacilli. Such a tuberculin might be called autogenous, and was suggested by Löwenstein,¹ in 1905. Krause,² in 1907, recommended an autogenous bacillary emulsion. Rothschild³ used autogenous tuberculins, and also polyvalent tuberculins; and the latter kind was used also by Rosenfeld.⁴

Chemistry.—The reader has now had a description of the method of manufacture of the best-known tuberculins. Those that are in widest clinical use have been specifically referred to. With a few exceptions, the tuberculins above named have been tested by animal experimentation, and for each it is claimed that a certain degree of immunization in animals can be effected by them. For a smaller number excellent results in human therapy are attested by their makers, or by friends of the latter. It would, however, be tedious and unprofitable to examine in detail the evidence that has been presented for their respective immunizing powers, since much of such work has been uncontrolled and the only experiments with some of the tuberculins have been conducted by the inventors, who should, in

¹ Löwenstein: Ueber Resorption und Immunitätserscheinungen. Eine Immunitätsstudie. Ztschr. f. Hyg. u. Infektionskrankh., 1905, li, 341.

² Krause: "Spezifisches" Tuberkulin. Ztschr. f. Tuberk., 1907, xi, 394.

³ Rothschild: Ueber Autotuberkuline. Ztschr. f. Tuberk., 1908, xii, 397.
Ueber Mischtuberkulin (Polygene Bazillen-Emulsion). Deutsch. med. Wehnschr., 1909, xxxv, 921.

⁴ For further references on the preparation of various tuberculins consult E. Loewenstein: Über Tuberkulinpräparate zu diagnostischen und Heilzwecken. Loc. cit. and Bandelier u. Roepke: Lehrbuch der spezifischen Diagnostik und Therapie der Tuberkulose. Würzburg, 1911.

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all kindness, be credited with a large amount of bias. So, although the methods of preparation have been presented with some detail, as illustrating the wide curiosity and the hopes and plans of many ardent workers, as regards the availability of the products we must content ourselves with the statement that by years of clinical work the more useful ones (from the point of view of human therapy) have crowded out the ineffective or those that are practically duplicates of the favorites. In brief, we are forced to the statement that the only reason we have for preferring a few of the tuberculins out of the many is the pure clinical reason that these few have been the survivors for preferment by clinicians. Contrarily, the remainder have been ineffective, poisonous, or close imitators of the preferred ones.

What are the criteria for admission to the class of tuberculins, if it is so difficult to differentiate between the merits and defects of so many different substances? How do we know that a substance is a tuberculin at all? It may be said at once that chemical analysis does not give us the solution. Chemical work with the tubercle bacillus itself, and particularly with tuberculins, has been so contradictory and, even when harmonious, so insufficient, that it is inadvisable to review the workers and their work. Those who wish to inform themselves of the fragmentary work that has been done with the chemistry of tuberculin we refer to the books of Ott,¹ and of Ruppel.²

The earlier workers with the tubercle bacillus did not sufficiently recognize the effect of the culture-medium upon the apparent composition of the bacilli. There is fair agreement as to the fatty bodies of the tubercle bacillus. The presence of cellulose in the capsule is in dispute. Alka-

¹ Ott: Die chemische Pathologie der Tuberkulose. Berlin, 1903.

² Ruppel: Über Tuberkulin und andere spezifische Präparate zur Erkennung und Bekämpfung der Tuberkulose. Berlin, 1909.

loids, reported by Hunter,¹ have not been proved. As regards the proteids, albumoses, albuminates, and perhaps peptones, have been found. The status of the phosphates is unknown. A tuberculosamin (a protamin) seems to exist, tied to a nucleinic acid known as Tuberculinic acid. However, it is not known to what substance the bacilli owe their specific action—whether to their metabolic deposits, or to something contained within themselves. It seems to be definitely settled that the specific component which can be extracted in various simple ways is not an albumose or a toxalbumin, since it stands high heat.

As regards the chemistry of tuberculin, what is found depends a great deal upon whether the tuberculin is derived from the fluid element of the culture, or from the bodies of the tubercle bacilli. However, the same specific substance seems to exist in material derived from either. But from this it cannot be concluded that the specific element is a secretion, since there is evidence pointing to the maceration and minute fragmentation of the bacillary bodies in any fluid culture (Wolff-Eisner).² And Römer³ has shown, too, that even simple watery fluid can extract the cell-contents of the bacillus. In a general way it may be said that albumoses and peptones have been found in the tuberculins prepared from culture-fluids. But these are not necessarily the specific substances, however closely the latter may be associated with them. So far no chemist has been able to identify the specific substance or substances with any one or more chemical components of either the bacillus or a tuberculin. At present we must, therefore, affirm recognition of a tuberculin, as such, to be

¹ W. Hunter: On the nature, action and therapeutic value of the active principles of tuberculin. *Brit. Med. Jour.*, 1891, ii, 169.

² Wolff-Eisner: *Frühdiagnose und Tuberkulose-immunität*. Würzburg, 1909.

³ Römer: *Darstellung und Wirkung proteinhaltiger Bakterienextrakte*. *Berl. klin. Wchnschr.*, 1891, xxviii, 1189.

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dependent not upon a chemical, but upon a biological, test. The biological test is the one described in Section I as the tuberculin reaction. The capacity of a substance to produce the specific reaction in a tuberculous focus within a short time after its administration in a minute dose, and the lack of any toxicity by the same substance, even in large doses, for animals or human beings that have never undergone a tuberculous infection, must at present be accepted as a sufficient reason for stamping such a substance as derived from the tubercle bacillus—or one of its close congeners—and as non-existent in other pathogenic organisms. By common usage, any preparation containing a substance capable of such specific, selective action upon tuberculous tissue is entitled to the name tuberculin. By adopting this common-sense view much confusion is avoided, as also much discussion concerning the relative values of certain tuberculins. For instance, Landmann maintains for his tuberculol that it is a more valuable preparation than Koch's tuberculin, because tuberculol is much more toxic to non-tuberculous animals. And indeed other authors of tuberculins have come to us with but little experimental or clinical evidence, and have maintained the superiority of their preparations over Koch's, principally on the score of their greater toxicity for healthy animals. Indeed even Bandelier and Roepke, in their excellent handbook, point to the high toxicity of tuberculol as an argument in its favor. It must now be evident to the reader that such arguments are entirely fallacious. Certainly any substance, whatever its nature or origin, that has desirable therapeutic effects should be promulgated; and as vigorously as possible. But to have a preference for one tuberculin over another because it is more toxic, and only for that reason, is to misunderstand the entire meaning of Koch's crucial experiment which resulted in the discovery of a specific substance that is exactly non-toxic. Of course,

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it is not to be assumed, *a priori*, that such a non-toxic specific reagent is therapeutically more potent than the toxic preparations. The fact is, however, that these specific substances have been selected because they have empirical value. The toxic substances have thus far brought us nowhere therapeutically, and certainly cannot claim our attention on the ground that they are toxic.

As regards the preparations which contain preëminently the specific substances, these, too, are many. No doubt some of these contain much less of the specific substance than the others. Or the specific substance may be multiple and the component proportions may vary; or the admixture of foreign, perhaps slightly toxic, substances may exist to a varying degree. This probably explains why immunity to one preparation does not carry with it immunity to another. For instance H. B. F. is apparently a more potent preparation than O. T., judging from the initial tolerated dose. Yet immunity to B. F. does not mean immunity to an equivalent dose of O. T. But, to a certain extent, immunization does occur reciprocally with many tuberculins (as judged by the cutaneous or subcutaneous reaction), and is a strong argument for the practical identity of numerous tuberculins.¹

In a later section shall be described the clinical results obtained with the various tuberculins, and the preference of one tuberculin over another will be discussed.

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In discussing the therapeutic results obtained by the use of tuberculins we shall temporarily ignore the numerous varieties. Our excuse for this is the great similarity between the effects of most of them, and the comparative inefficiency of nearly all the rest. We shall, therefore, at

¹ See Part I, p. 52.

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first, speak of the results obtained in pulmonary tuberculosis by no matter what tuberculin, and we shall later discuss the specific applicability (if there be any) of the various brands. And then, too, will be taken up the therapy of tuberculosis other than pulmonary and the use of favored varieties in these forms.

Animal Experiments.—If we consider the results of experiments on animals, it is not because we must be bound by the evidence obtained from them. Certainly tuberculosis in guinea pigs is not clinically that of man. Nor is the experimental infection of larger animals always comparable to the mode of infection in human beings. And we have reason to think that there are generic differences in the serological and cytological immune reactions, as much as in the gross anatomy. But contributory evidence is interesting and perhaps valuable. At any rate, that animals can be protected prophylactically and affected curatively by tuberculin has been an argument adduced by nearly every inventor of a tuberculin. Koch himself fortified his hopes as to his Original Tuberculin by citing animal experiments.

As pointed out in the previous section, he thought that he had been able to prolong the life of, and even to cure, infected guinea pigs by his tuberculin. Later workers have been unable to obtain equally good results, not even when using T. R. or B. E. Baumgarten and others have been unable, by tuberculin, to get any good results at all. Jürgens,¹ however, notes favorable changes in animals, and Béranek claims excellent results with his tuberculin. In this country Trudeau² speaks favorably of the influence

¹ Jürgens: Experimentelle und klinische Untersuchungen über Tuberkulin. *Ztschr. f. exper. Path. u. Therap.*, 1905, i, 519.

² Trudeau: Artificial Immunity in Experimental Tuberculosis. *New York Med. Jour.*, 1903, lxxviii, 195.

Antibacterial or Antitoxic Immunization in Tuberculin Treatment. *Jour. Am. Med. Assn.*, 1909, lii, 261.

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of tuberculin in tuberculous guinea pigs, and Pearson and Gilliland¹ have seen encapsulation of the lesions of treated cattle, although living tubercle bacilli remained in such lesions. On the whole, there is general admission that in animals the best results are obtained by living vaccines,² and that by tuberculins bacterial immunity is not attained. Many workers do claim for tuberculins, however, that by the use of them life is prolonged, the development of virulent lesions hampered and the healing of slight lesions furthered. However, many of the experiments have been confined to regretfully few animals, and, owing to the numerous tuberculins, there have been comparatively few attempts by unbiased observers to test the claims of the proud inventors of "newer and better" tuberculins. Those that did not believe did not use the tuberculins. Those that did believe, in most cases, believed so well that they accepted the animal data as sufficiently prolix, and proceeded at once to put the drug at the disposal of their human wards. And the results obtained by the human test establish one thing—that the usefulness of a tuberculin and, indeed, of the whole group must rest on the results obtained at the bedside. Whatever the sources from which hints, plans or suggestions are obtained, it is the clinical data by which tuberculin therapy must stand or fall. And it is to these data that we must now address ourselves.

Clinical Statistics of the Result in Pulmonary Tuberculosis.—It is true that the results obtained in the first years after Koch's announcement of his cure are not merely discouraging but actually repulsive. It is, however, no less true that to quote the data of those years as contraindicating the modern tuberculin therapy is to argue one's self

¹ Pearson and Gilliland: Some experiments upon the immunization of cattle against tuberculosis. *Proc. Path. Soc., Philadelphia*, 1902, vi, 105.

² Webb and Williams: Immunity in tuberculosis. *Jour. Med. Research*, 1911, xix, 1.

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either unaware of the differences between the two eras or hopelessly biased. One might as well declare a trans-Atlantic voyage tedious because it took Columbus months to cross the ocean. Not only were Koch's cautions as to the selection of cases ignored or misunderstood, but he himself used a method of procedure which is now nowhere in vogue. What the differences are will be explained in a later section. Here we wish to state emphatically that our argument is for the use of the tuberculin on a plan guided by present knowledge. However interesting the historical data are, they need not be mentioned here. Here we wish to know what are the results therapeutically with tuberculin as it is now used, restricted to patients that we now deem fit, applied in doses that we now deem safe, and graduated to obtain effects which we now know are not only harmless but attainable. Not only must we restrict our arguments to the modern data, but we must accept in evidence only the statements of those who have used tuberculin and not of those who, thinking it dangerous, have never tried to use it.

Upon a discriminating inspection of the evidence brought to us by the users of tuberculin one deduction is salient: tuberculin is not a "cure" of tuberculosis—no more than hygiene or rest or diet or climate, or any other favorable factor. And, in making this comparison, we have really stated what tuberculin is—not a "cure," but a favorable factor. Whether it is a more or less favorable factor than rest or fresh air, for instance, will probably never be known. Such things cannot be weighed. Until we find some one thing that, in itself, and without any other measures, can cure, until that time we cannot afford to ignore any helpful factor. That tuberculin is so helpful the following evidence leads us to believe. The healing effect of tuberculin being one of gradual stimulation, and not usually a sudden process, the evidence for its efficacy can, in

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consequence, not be composed, to any considerable extent, of the citation of sudden cures. Since healing, with or without tuberculin, takes place only after the lapse of years, the measure of the favorable influence of a course of tuberculin that has lasted perhaps only six months is in its nature difficult. While evidence attesting the sudden improvement of patients upon the administration of tuberculin is gratifying, and not at all rare, we must look carefully for some other direction in which to gather the bulk of the testimony. We must prepare to seek the truth in a painstaking comparison covering a long period of time, of certain well-selected factors in the condition of similar patients treated with and without tuberculin, under otherwise the same circumstances. Moreover, it is advisable to have as large a number of patients as possible reported by the same observer. The fulfillment of this requirement leads us away from the report of individual cases to the study of the reports of institutions where large numbers of patients with pulmonary tuberculosis are aggregated—in other words, to sanatorium or hospital statistics. Here only do we get many patients under a system both of observation and of treatment that is capable of being unified and standardized. However, that such standardization is possible does not mean that it has been accomplished.

The inherent difficulties of an acceptable classification of pulmonary tuberculosis are notorious, and have been excellently summarized by Turban. The problem is to devise a nomenclature which shall briefly, by the application of a symbol, epithet or short phrase, indicate accurately the clinical and anatomical condition of a patient and his chances for recovery or life. The problem has not been solved. This is not the place to discuss the matter at length. Briefly, the difficulty arises from the lack of correlation between the anatomical extent of the disease and

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its clinical extent, as judged by the symptoms at the time of classification and the course of the disease subsequently. Two patients with apparently the same physical signs over a corresponding portion of the chest may be wide apart, not only in their chances for recovery, but in their state of health. Indeed one may feel and look well, while the other may be subjectively and evidently sick. Obviously the difference between the physical signs presented by the same patient upon admission to and discharge from the sanatorium cannot be taken as the measure of the patient's improvement or deterioration during his residence. It is quite possible that considerable healing has occurred without any diminution of the physical signs, and it is just as possible that a diseased area has become more thoroughly involved without any apparent change in the signs. Especially does the truth of this statement appear when we realize that the findings upon discharge must be compared with no more than a written record of the findings upon admission. Add to this difficulty the subjectivity of a physical examination made upon a patient to be classified upon the basis of his improvement under treatment, and it is manifest that the physical signs in pulmonary tuberculosis are a treacherous foundation for a statistical evaluation of a treatment of that disease.

What vitiates such statistics particularly is the difficulty of studying early lesions. In the diagnosis of early or minute lesions there is room for considerable abuse, whether conscious or unconscious. Sanatoria that desire to present impressive statistics naturally lean toward the admission of incipient cases. Unfortunately physical signs should play only a minor part in the diagnosis of a slight lesion. The emphasis should be laid upon the discovery of signs of the activity of a lesion and not upon the lesion itself, as has been pointed out in the section on diagnosis (pp. 109 and 186). This has often not been done, and many

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patients have been admitted to sanatoria in whom it would have been rank ingratitude not to get well. These figure as cures—with or without tuberculin. But it is unfair to admit into any inquiry concerning the efficacy of tuberculin—or any treatment—such incipient cases as are diagnosed by the physical signs only, since some of these may not have been sick, to begin with. However, since tuberculin, or any other remedy, cannot be expected to do its best with far-advanced cases, it is also unfair to throw out of the calculation all early cases—a group in which good results can fairly be expected. We must, therefore, conclude that no statistics that are based chiefly on the physical signs can be admitted into our inquiry.

Nor can we use the symptoms as a safe guide. For example, a patient, moderately advanced, may become afebrile and comfortable, may even cease coughing, and yet may relapse shortly after leaving the sanatorium. It is unfair to balance him against an equally comfortable patient whose disease remains arrested for years after his discharge. As it is the boast of tuberculin advocates that it is especially in the lasting results that the efficacy of tuberculin is most evident, we must admit the injustice of employing the symptoms registered upon the discharge of the patient as a basis for the statistics of a therapeutic inquiry. Of course, generally speaking, patients who feel well are in better condition than those who feel sick, but when we note how often temporary improvement occurs in sanatorium patients we must reject studies of results that are based on symptoms.

In order to rid their result-figures of the objections above stated, institutional workers have resorted to three methods other than the physical signs or the symptoms. These are: 1. Working ability. 2. Duration of life. 3. The presence of tubercle bacilli in the sputum.

The working ability of a patient is assumed by many

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to be a reliable basis for the estimation of the amount of healing. The argument is that the more healing there has been, the more hours a day the patient can work, and the more years after his discharge will he be able to work. As a variation of this method, the earning capacity has been taken as a guide rather than the working ability, as judged by the patient himself. However, neither the working ability nor the earning capacity are free from objection. Both may be strongly influenced by temperament and social status. There are lazy patients, and timid patients, who think they cannot work when they really can; and there are stubborn, bull-dog men who will work to the last hour of their life. To judge either of these by the written reports they send in about themselves after they have left the sanatorium is not to know human nature.

An extremely objective measure, and an excellent standard of late results, is the Duration of Life. After all, whatever the signs or symptoms, that's the crux of the thing. The treatment that adds the most years to a patient's life is, in all probability, the most efficacious treatment. Unfortunately it takes years for the results to be evident. Up to this time very few of the sanatoria have made their tuberculin reports upon this basis. Such figures are naturally hard to gather, but they should be gathered. It is to be hoped that in the future more tuberculin statistics will be expressed in this form. We shall use such of these figures as are available, but must base our main argument, as to the results on discharge, upon the sputum examinations.

The presence of tubercle bacilli in the sputum is an objective fact. With ordinarily careful examination by competent men the results are rid of subjective doubt. Moreover, if only patients expectorating tubercle bacilli are admitted into the statistics, there is no doubt that they have pulmonary tuberculosis in an active form (only most

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exceptionally is such a case not active) and, if in such an open case of pulmonary tuberculosis the bacilli disappear from the sputum, it is practically certain that a definite improvement has occurred. If the bacilli disappear more uniformly and in less time under one form of treatment than under another, we can be sure the former has decided advantages. While figures based on the disappearance of bacilli from the sputum are not as fundamental as those based on the duration of life, the former have the advantage of being more easily gathered during a short period, and are, of course, alone applicable to the study of the condition of patients on discharge. Moreover, a larger number of patients can be listed, since after leaving the sanatorium many patients are lost to the records. It goes without saying that the sputum examination must be frequent and thorough before a negative report can be rendered. It is gratifying to note that a number of reports are at hand dealing with large numbers of patients, based on the sputum statistics.

With this understanding of the relative value of figures as to results coming from various sources, we are ready to note the statistical evidence.

The bad results following the early work of Koch have been well summarized by Guttstadt¹ and Thorner.² We are not particularly concerned with these reports, since we are interested only in the results of those who have used tuberculin by the modern methods. We need notice them only to show that they are decidedly confirmatory of the specific action of tuberculin on tuberculous tissue—an action which may be benign or malign, as the user wishes.

Even during that reign of darkness not a few careful

¹ Guttstadt: Die Wirksamkeit des Kochschen Heilmittels gegen Tuberkulose. Zusammenstellung der Berichtsergebnisse. Klin. Jahrb. Ergänzungsband. Berlin, 1891, p. 843.

² Thorner: Zur Behandlung der Lungentuberkulose mittels Kochscher Injektionen. 1894.

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observers had come to know that tuberculin can be used without danger to the patient; and these, after so using it, came to be more and more convinced of the healing effect of tuberculin. To these men belongs the credit of having kept cool heads during a panic. They are to be honored for having realized that because tuberculin was being misused was not a reason for throwing it away—but a reason for using it correctly. Among these men were Ehrlich and Guttman,¹ Biedert,² Lichtheim,³ Aufrecht,⁴ Fraenkel,⁵ and Trudeau⁶ in our own country. Goetsch,⁷ in 1901, published the first large summary. From that time the number of those using tuberculin has increasingly grown, in spite of fierce attacks from academic opponents—grown not only in one country, but everywhere, not only in hospitals, but in sanatoria, dispensaries and private practice. (See introduction of Bandelier and Roepke's book.) We emphasize the number of reports because if, year after year, a substance is violently attacked as either dangerous or useless, and if, despite such attacks, there come from everywhere reports increasingly numerous of positively favorable results, while, on the other hand, there is almost a complete disappearance of reports evidencing any dangers, we are forced to the conclusion that clinicians are finding for themselves that tuberculin is helpful. Among such names

¹ Ehrlich u. Guttman: Die Wirksamkeit kleiner Tuberkulindosen gegen Lungenschwindsucht. Deutsch. med. Wchnschr., 1891, xvii, 793.

² Biedert: Diskussion-Bemerkung. Vereinigung niederrhein-Westfäl. u. südwestdeutscher Kinderärzte in Wiesbaden, 1909.

³ Lichtheim: Das Koch'sche Heilverfahren. Deutsch. med. Wchnschr., 1891, xvii, 273.

⁴ Aufrecht: Robert Koch's Tuberculosenbehandlung. Deutsch. Arch. f. klin. Med., 1892, xlix, 1.

⁵ Fraenkel: Ueber die Anwendung des Kochschen Mittels bei Tuberkulose. Berl. klin. Wchnschr., 1891, xxviii, 185.

⁶ Trudeau: Tuberculin immunization in the treatment of pulmonary tuberculosis. Am. Jour. Med. Sc., 1907, cxxxiii, 813.

⁷ Goetsch: Ueber die Behandlung der Lungentuberkulose mit Tuberkulin. Deutsch. med. Wchnschr., 1901, xxvii, 405.

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we may recall Amrein,¹ Aufrecht, Béraneck, Brown,² Denys, H. Engel,³ Hammer,⁴ Hawes and Floyd,⁵ Heron,⁶ Jochmann, Kartulis,⁷ Kehl,⁸ Klebs, Krause, Kremser,⁹ Langenbach u. Wolff,¹⁰ Mitulescu, Moeller,¹¹ Nagel,¹² Neumann,¹³ Nourney,¹⁴ Paquin,¹⁵ Petruschky,¹⁶ Philippi,¹⁷ Pottenger,¹⁸ Raw, Rayewsky,¹⁹ Rumpff, Saat-

¹ Amrein: Weitere Tuberkulin-Erfahrungen. Beitr. z. klin. d. Tuberk., 1907, viii, 327.

² L. Brown: In Klebs: Tuberculosis. New York, 1909.

³ H. Engel: Zur Entfieberung Tuberkulosen durch Kochscher Alttuberkulin. München. med. Wehnschr., 1910, lvii, 1742.

⁴ Hammer: Die Tuberkulinbehandlung der Lungentuberkulose. München. med. Wehnschr., 1906, liii, 2343.

The value and practicability of the use of tuberculin in pulmonary tuberculosis. Internat. Tuberculosis Congress, Washington, 1908, i, Pt. 2, 739.

⁵ Hawes and Floyd: The tuberculin treatment of dispensary patients. Boston Med. and Surg. Jour., 1910, clxii, 1.

⁶ Heron: Ueber den diagnostischen und therapeutischen Wert des Tuberkulins. Ztschr. f. Tuberk., 1901, ii, 447.

⁷ Kartulis: In Festschrift für Robert Koch, Jena, 1903.

⁸ Kehl: Über die kombinierte Anwendung von Alttuberkulin und Neutuberkulin. Med. Klin., vi.

⁹ Kremser: Tuberkulinbehandlung: I Versam. der Tuberkuloseärzte zu Berlin, 1904, p. 35.

¹⁰ Langenbach u. Wolff: Ueber die Tuberkulinbehandlung in 99 Fällen von Lungentuberkulose. Deutsch. med. Wehnschr., 1891, xxxvii, 935.

¹¹ Moeller: Ärztlicher Jahresbericht für das Jahr 1904. Ztschr. f. Tuberk., 1905, vii, 329.

¹² Nagel: Tausend Heilstättenfälle (In der Lungenheilstätte Cottbus). Beitr. z. klin. d. Tuberk., 1906, v, 451.

¹³ Neumann: Beiträge zur spezifischen Behandlung der Tuberkulose auf Grund klinischer Beobachtungen. Beitr. z. klin. d. Tuberk., 1910, xvii, 69.

¹⁴ Nourney: Verein der Aerzte Düsseldorfs. Referat. Deutsch. med. Wehnschr., 1905, xxxi, 47.

¹⁵ Paquin: In what treatment may the tuberculous have confidence? A word about standardizing tuberculin. New York Med. Jour., 1911, xciv, 89.

¹⁶ Petruschky: Der gegenwärtige Stand der Tuberkulinbehandlung. Leipzig, 1901.

¹⁷ Philippi: Die Lungentuberkulose im Hochgebirge (Davos), 1906. Stuttgart.

¹⁸ Pottenger: The diagnosis and treatment of pulmonary tuberculosis. New York, 1908.

¹⁹ Rayewsky: Observations on the use of tuberculinum purum in pulmonary tuberculosis. New York Med. Jour., 1911, xciv, 973.

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hoff,¹ Sahli, Schmoeller,² Trudeau,³ Turban,⁴ Ure,⁵ v. Ruck,⁶ Wilkinson,⁷ Wolff-Eisner.⁸

Many more names from at home and abroad might be cited. We cite them as observers only, and purposely refrain from quoting their statistics. For reasons above stated we think it unfair to adduce in evidence their figures, however large. Having once decided that the statistics were not uniformly compiled, the patients not uniformly classified, it would be a logical sin to yield to the temptation of quoting them. We use these names here simply as an indication of the trend of sentiment among individual workers, no more and no less. We think it only fair to attribute to them a certain force, especially in view of the decreasingly small number of negative results. They are witnesses to the good character of tuberculin, who, although they have not taken careful notes, are competent to testify on account of their working familiarity with the subject. They lend strong support to the figures that are to follow. We hope that future publications will contain more figures on the sputum results and on the duration of life. But the figures now extant are by no means insignificant. Not only are they large, but many come from the same clinic, comprising cases studied by the same observer.

¹ Saathoff: Die spezifische Erkennung und Behandlung der Tuberkulose. München. med. Wehnschr., 1911, lviii, 2544.

² Schmoeller: Theoretisches und Praktisches ueber Immunisirung gegen Tuberkulose. Strassburg, 1905.

³ Trudeau: The therapeutic use of tuberculin combined with sanatorium treatment of tuberculosis. Am. Jour. Med. Sc., 1906, cxxxii, 175.

⁴ Turban: Ueber Tuberkulin- und Heilstättenbehandlung Lungenkranker. Cit. nach Freymuth. München. med. Wehnschr., 1903, 1, 1875.

⁵ Ure: A plea for the early diagnosis and treatment of incipient phthisis by tuberculin. Australasian Med. Gazette, 1911, xxx, 20.

⁶ K. and S. v. Ruck: A clinical study of 292 cases of pulmonary tuberculosis. Therap. Gaz., Detroit, 1911, xxxv, 768.

⁷ Wilkinson: Tuberculosis and tuberculin. Brit. Med. Jour., 1911, i, 264.

⁸ Wolff-Eisner: Die Tuberkulinbehandlung der Tuberkulose und die Klimatotherapie im Rahmen derselben. Med. Klin., 1911, vii, 1236.

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And the significant fact is that these carefully studied figures affirm the incomplete conclusion of the observers cited above. Together the two lists comprise a mass of respectable evidence. It comes from men who have worked with tuberculin for years, and who have convinced themselves, although some of them were at first strongly skeptical.

Reliable statistics covering life-duration are those from Saranac. They cover a space of 15 years, and show that the tuberculin cases do better; especially the moderately advanced. In the incipient class the balance in favor of the tuberculin-treated is not large.¹ However, many of the incipients never had positive sputum. Heron and Rembold² have had similar results.

We now present the sputum statistics, figures which,

¹ The exact figures are shown in the following table from Brown's chapter in Klebs: *Tuberculosis*, p. 560:

| ULTIMATE RESULTS | | |
|------------------------|--------------------|-----------------------|
| | With Tuberculin | Without Tuberculin |
| Incipient: | | |
| Apparently cured | 88 | 78 |
| Disease arrested | 77 | 78 |
| Active | 33 | 27 |
| Moderately advanced: | | |
| Apparently cured | 91 | 86 |
| Disease arrested | 48 | 45 |
| Active | 41 | 22 |

“The ultimate results, expressed in percentages of those living one to fifteen years after discharge, proper allowance being made for the varying numbers in each year and class.”

See also Brown: A study of the cases of pulmonary tuberculosis treated with tuberculin at the Adirondack Cottage Sanitarium. *Ztschr. f. Tuberk.*, 1904, vi, 235.

² Rembold: Dauerresultate mit Alttuberkulin. *Deutsch. med. Wehnschr.*, 1897, xxiii, 581.

Zur Heilwirkung des Tuberkulins bei Lungentuberkulose. *München. med. Wehnschr.*, 1898, xiv, 681.

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from their objectivity and their almost indubitable meaning, are extremely valuable. They speak strongly for the healing effect of tuberculin.

Kremser chose 110 patients expectorating tubercle bacilli, treating 55 of them with tuberculin. The patients were not selected, but were placed in the groups alternately as they were admitted. Of those treated with tuberculin 22, or 40 per cent., lost the bacilli; of those treated without tuberculin only 16, or 29 per cent.

Philippi finds that in his II stage cases 58 per cent. of those treated by tuberculin, against 19 per cent. of the untreated, were rid of bacilli in the sputum; and in the III stage cases 31 per cent. of the treated, as against only 7 per cent. of the untreated.

Turban reports that of 86 open cases treated by tuberculin 47.7 per cent. lost their bacilli. Of 24 untreated, only 27.4 per cent.

Brown reports from Saranac that in the incipient class 67 per cent. of the tuberculin patients were rid of bacilli; of the others, 64 per cent. In the moderately advanced the figures are respectively 44 per cent. and 24 per cent.

Bandelier¹ reports 500 cases, of whom 202 had tubercle bacilli in the sputum. On discharge, after an average treatment of five to six months, 129, or 63.9 per cent., had the sputum changed from positive to negative. Twelve were in Stage I; of these 100 per cent. became negative. Of the 79 in Stage II, 87.3 per cent. became negative. Of the 113 in Stage III, 50 per cent. became negative. Bandelier challenges the production of similar results without tuberculin, and says they are unparalleled in the literature. These figures are remarkable, yet they are based on a respectable number—202 cases.

¹ Bandelier: Die Leistungsfähigkeit der kombinierten Anstalts- und Tuberkulinbehandlung bei der Lungentuberkulose. Beitr. z. klin. d. Tuberk., 1910, xv, 1.

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It is important to note that these percentages are closely paralleled by those of E. Löwenstein,¹ who quotes the gratifying number of 682 open cases. No case is reported that did not reach the dose of 10 mg. O. T. Four sputum examinations were required to establish a case as negative. Under the tuberculin treatment 361 of the 682 cases finally showed negative sputum—a percentage of 53. Such a result, he maintains, cannot be obtained in any other way than by tuberculin. His analysis of the results of 20 years of hygienic-dietetic cure without tuberculin gives only 15 per cent. of the discharged as having no bacilli in the sputum.

The striking figures on the sputum, coming as they do from competent observers, dealing not with compilations but with their own material, are significant and important. The percentages are not dubious, but are heavily in favor of tuberculin, and form an excellent reason for the furtherance of tuberculin therapy. The conversion of an open infectious case to a closed—therefore much less infectious—case would in itself justify the use of tuberculin.

Bandelier has classified the 500 cases above referred to, containing 202 open cases, also from the point of view of work-capacity. Compared with the sputum results, the figures are:

| | Total | Stage I | Stage II | Stage III |
|----------------------------------------------------|-----------------------------|-----------------|----------------|----------------|
| Complete Earning Capacity on Discharge..... | 500 Cases 69.8 per Cent. | 90.4 per Cent. | 80.7 per Cent. | 32.8 per Cent. |
| Sputum Changed from Posi- tive to Negative..... | 202 Cases 63.9 per Cent. | 100.0 per Cent. | 87.3 per Cent. | 44.0 per Cent. |

It is seen from the table that statistics based on the sputum becoming negative afford a real evidence of im-

¹ Löwenstein: Tuberkulinerfolge bei 682 offenen Lungentuberkulosen. Deutsch. med. Wehnschr., 1910, xxxvi, 1654.

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provement, even when that is judged from the purely symptomatic side. The parallelism between the two sets of figures is close, and forms an additional argument for taking the bacillary content of the sputum as a statistical basis.

Effect of Tuberculin on the Pathological Anatomy.

—Having recorded the gross results which lead those clinicians who have used tuberculin to believe that it is a favorable factor in the treatment of pulmonary tuberculosis, it is appropriate to discuss in a more analytical way the details of the results obtained by tuberculin. In an analysis of this sort we are confronted with the difficulty of assigning to any one of several concurrent therapeutic measures its own specific effect. Here we are especially liable to bias. We must warn the reader from the beginning that such evidence is necessarily, to a large extent, impressionistic, especially so when we speak of symptoms. Not that symptoms are not improved or removed, but the impressionistic element asserts itself in assigning so and so much of the results to tuberculin rather than to the rest or the fresh air, or to the adequate diet (unless a large number of cases are studied in reference to each symptom or sign, as has been done with the question of positive sputum). However, this evaluation has no bearing on the argument that tuberculin plus other therapy is more effective than other therapy without tuberculin. That remains a fact inferred from sufficient evidence, no matter how wrong or right be our opinion as regards the quantitative effect of tuberculin on any one symptom or sign. With this caution clear we may proceed.

What do we know of the effect of tuberculin on the pathological anatomy of the tuberculous lesion? Can we demonstrate a direct effect on the lung tissue itself? As stated in the section on diagnosis, during a reaction there is much hyperemia at and around the affected focus. Al-

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though in therapy we do not elicit constitutional reactions, we know from observations on lupus and on tuberculous laryngitis that mild reaction may occur at the focus, even when no constitutional reaction has resulted. These mild reactions, it is fair to state, promote fibrosis. At any rate, the end-results, as seen in lupus, are fibrosis and healing. Virchow¹ maintained the opposite, basing his opinion on the autopsy of a patient dying under tuberculin treatment. He found acute inflammation with apparently newly infected areas in the lungs. However, he himself later declared it an unjustifiable inference to attribute the dissemination to tuberculin, since he found the same appearance in untreated patients. Moreover, this patient was being treated by the method of violent reactions. Indeed, if the observation of Virchow be of any value in this discussion, it is rather to attest the efficacy of tuberculin in producing hyperemia, and this hyperemia need not be excessive, if the reactions induced are mild.

Koch believed that tuberculin had a direct necrotizing effect on tuberculous tissue. He conceived that with each reaction more and more tuberculous tissue was necrotized, so that, finally, in some cases, tuberculin reactivity ceased on account of the absence of any tissue capable of necrotization. Later work made it impossible to conceive of the healing effect of tuberculin as being due to a necrosis. Spengler² was among the first to deny a necrotic effect and to postulate an inflammatory change at the focus of reaction. Ziegler³ has made thorough and extensive studies of the anatomical changes, and in his results there is now

¹ Virchow: Aus dem pathologischen Institut. Bericht des Directors, Professor Dr. Virchow. Klin. Jahrb. Ergänzungsband, 1891, p. 264.

² C. Spengler: Festschrift für Robert Koch, Jena, 1903.

³ Ziegler: Ueber das Koch'sche Heilverfahren bei Lungentuberkulose und anderen inneren tuberkulösen Erkrankungen. Pathologisches-Anatomisches. X Kongr. f. innere Medizin, 1891, p. 130 (Verhandlungen, J. F. Bergmann, Wiesbaden).

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general concurrence. It must be considered as proved that, in the event of a focal reaction, what occurs at the focus is a hyperemia with stasis and extravasation of formed and unformed elements from the blood. The question Ziegler particularly studied is the prolonged effect of tuberculin when given, not in diagnostic doses, but in the comparatively small therapeutic doses over a long interval. He concludes definitely that tuberculin causes no necrosis, but, in consequence of the inflammation, either a resorption of tuberculous tissue or a fibrosis around it. Tissue around the tubercle may liquefy and the tubercles themselves, being flooded with serum and phagocytes, may be resolved and removed, or, if they are too massive, the inflammation results in an encapsulation of the mass, which is now become a foreign body, although potentially a dangerous one, containing, perhaps, living tubercle bacilli. The more intense the reaction the more likelihood of greater absorption, and perhaps of dissemination of toxic and infectious material. More in detail, his results show that not all of the tuberculous foci in the body react at the same time. In fact, only a comparatively few of the tubercles present in the body at any time react after any one dose. Nor do those that react do so to an equal degree, the effect of a dose of tuberculin being, therefore, incalculable, both as regards the inclusiveness of foci and its extent at any focus that happens to be involved. The view of Petruschky¹, that the foci are generally and extensively involved, can not be held. The net result of Ziegler's study of autopsy material can be summed up in the statements that such material does not show any changes around the tuberculous tissue indicative of a dangerous reaction, when tuberculin is given for treatment, cautiously; and that on the other hand there is no evidence of the existence of a heal-

¹ Petruschky: Koch's Tuberculin und seine Anwendung bei Menschen. Berl. Klin., 1904, Ht. 188, 1.

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ing process other than that seen to occur without tuberculin. The natural healing of tuberculosis proceeds only somewhat by absorption and largely by fibrosis or encapsulation, more or less perfectly. Tuberculin produces the same effect, as attested by Ziegler, Kromayer,¹ Spengler, Rindfleisch,² Schimmelbusch,² Heubner,³ Pearson and Gilliland, Trudeau, Rohmer,⁴ and others. The question then suggests itself, if the healing with and without tuberculin is qualitatively the same, is there any quantitative difference? The opinion of Ziegler is that there is a greater tendency to fibrosis in those treated by tuberculin than in those not so treated. Petruschky⁵ and Rohmer note unusually heavy fibrosis in the tuberculin cases. Pearson and Gilliland note the same in animals, as does Jürgens. Neumann,⁶ on the basis of a gross and microscopic study of forty-six lungs, finds in the tuberculin-treated more fibrosis and an absence of infiltrative bronchopneumonia around the tuberculous areas. At the same time there seem to be fewer tubercle bacilli in the tissues. Köhler, who is an ultra-sceptical but therefore extremely useful critic of tuberculin therapy, notes there is less calcification in those treated by tuberculin. This has been noted also by Petruschky and Kromayer. Neumann has found also less caseation. All the authors, however, agree on the presence of more fibrosis than is usual in the untreated.

The relative absence of calcification may, therefore, be

¹ Kromayer: Histologische Mittheilung über die Wirkungsweise des Tuberkulins. Deutsch. med. Wchnschr., 1891, xvii, 305.

² Cit. Köhler: Tuberkulin und Organismus, Jena, 1905.

³ Heubner: Ueber das Koesche Heilverfahren bei Lungentuberkulose und anderen inneren tuberkulösen Erkrankungen. Ueber die Anwendung des Tuberkulins im Kindesalter. X Kongr. f. inn. Med., 1891, p. 139.

⁴ Rohmer: Tuberkulose und Tuberkulintherapie im Säuglings- und Frühen Kindesalter. Arch. f. Kinderh., 1911, lv, 51 and 97.

⁵ Petruschky: Ueber Heilstätten und Tuberkulinbehandlung. Leipzig, 1901.

⁶ Neumann: Loc. cit., p. 249.

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interpreted as an evidence of the healing influence of tuberculin—there being more resorption and encapsulation and, therefore, less need for calcification. Reviewing the evidence from the pathological anatomy, we see that it furnishes all the evidence that we have a right to expect. It indicates that tuberculin is not a brilliant remedy, but an agent that stimulates the usual healing to take place more rapidly than it otherwise would. That just this much has been noted by observant pathologists and not more is confirmatory of the clinical evidence and strengthens the clinical attitude. It is only fair to point out that the nature of the human autopsy material is necessarily such as to make the cause of tuberculin weaker rather than stronger, since where the therapy has been most successful the material is not obtainable. It is here cited, not to take the place of clinical results—which must remain the standard of measure of tuberculin utility—but to point out that it substantiates the fact that, by using tuberculin, no dangerous, uncontrollable element is added; but the natural processes of resorption and fibrosis (with the attendant immune changes) are mildly stimulated to somewhat greater activity, and that, in so far as anatomy can bring evidence, it is favorable to tuberculin. As regards the more violent changes attending strong reactions (such as were formerly used), these have been discussed in a section on the dangers of tuberculin.

More specific evidence (than that above given) of the anatomical effect of tuberculin we really cannot expect, since healing, whether it occurs under the action of specifics or under the persuasive influence of hygiene and nourishment, may reasonably be expected to proceed in about the same manner—that is, excluding the effect of a rapidly working agent which would cause a resolution (as in pneumonia). But we do not know of any such rapidly acting agent in tuberculosis. After all, the question resolves it-

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self, not into what we find at autopsy, but into what clinical facts we have bearing on the rapidity with which a lesion heals, and also on the permanency with which it heals.

Effect of Tuberculin on the Physical Signs.—We know that tuberculosis heals with difficulty. We know, too, that lesions which are apparently healed may harbor living tubercle bacilli for years and even decades. We have not ourselves ever been able to observe in patients treated by tuberculin—or treated in any other way—any disappearance of physical signs, such as is claimed by some authors. The clearing up of physical signs, unless the lesion from the very first presents only the slightest, barely perceptible physical signs, is a very slow process. If the lesion has passed just beyond the very incipient stage, râles disappear with the greatest slowness and perhaps never (indeed the facts almost justify the statement of Tripier¹ that if the lesion once presents physical signs the lesion is incurable). So stubborn are the physical signs, so persistent, that sanatoria have been driven to other criteria in order to decide the arrest of a case, e. g., the absence of tubercle bacilli from the sputum, or the patient's working capacity. We base our belief as to the effect of tuberculin upon lung lesions, however, on changes which, though slow, we are not accustomed to see in patients not receiving tuberculin. We feel justified in attributing an effect to tuberculin when we see a city patient in an advanced progressive stage becoming suddenly arrested and showing a gradual, although slow, diminution of the râles (e. g., Phipps, No. 5024). However, such evidence is not strictly quantitative, and we again point out that the value of tuberculin treatment must be gaged by the statistics given in the previous section—admitting that in pulmonary tuberculosis the evidence from pathological anatomy is necessarily meager. Yet from the

¹ Tripier: *Études anatomo-cliniques, cœur-vaisseaux-poumons*. Paris, 1909.

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same source there is no evidence against tuberculin. Moreover, there is confirmatory evidence of the healing effect of tuberculin when it is applied to the treatment of organs more accessible to inspection than the lungs. And it is only fair to assume an analogy, especially when that analogy is supported by the course of the disease.

Effect of Tuberculin on the Serum.—The subject of tuberculin immunity and tuberculosis immunity has already been discussed. It will here be adverted to in so far as it is directly connected with the question of the therapeutic effects of tuberculin. In so far as tuberculin helps a patient to get better it furnishes an element of tuberculosis immunity. In the majority of cases such a change for the better is associated with the development of a tolerance for tuberculin. This is a clinical fact, whatever our theories may be as regards the desirability or undesirability of tuberculin sensitiveness or insensitiveness. That the mere fact of a tolerance for tuberculin, in itself, as a factor isolated from all other clinical data is not necessarily a sign of improvement is obvious when we recall that an advanced, progressive case is tolerant of tuberculin, as far as regards an objective reaction. On the other hand, individuals very sensitive to tuberculin may have only the slightest lesion, and enjoy good health.¹ Evidently the controlling influences are complex. But we must not blind ourselves to the well-attested clinical observation that the average tuberculin patient shows, simultaneously with his improvement under tuberculin, a tolerance for tuberculin by whatever route. This remains a fact generally true, in spite of the citations of individual cases showing departures from this rule (e. g., Neumann's), and in spite of oscillations of theories of immunity. That varying factors are at work in individual cases is no doubt true,

¹ Geszti: Was geschieht mit dem im Körper produzierten Tuberkulin? Berl. klin. Wehnschr., 1911, xlviii, 292.

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but we are at present ignorant of them. In all cases tuberculin is to be given cautiously until further knowledge may point a better way. It is wrong to make desperate efforts to break down tuberculin sensitiveness or to develop it. Certainly by giving tuberculin cautiously, to tolerance, neither the sensitive nor the insensitive patient is harmed.

In the light of present knowledge, to argue from the presence or absence of opsonins, agglutinins, or anti-tuberculin, as to the therapeutic value of tuberculin, is premature. The data are insufficient.

Koch, Bandelier and Roepke, and others, have found specific agglutinins in tuberculin patients. Wright's opsonins are too variable, especially in tuberculosis, to merit discussion here.¹ Löwenstein and Pickert² find anti-tuberculin in patients doing well, whether or not treated by tuberculin. Wassermann and Bruck³ find anti-tuberculin in the blood of treated patients, while Wolff-Eisner,⁴ Czaska⁵ and Cohn⁶ do not. On the other hand, Strauss and Weil⁷ find anti-tuberculin in the blood, without tuberculin tolerance. Bauer and Engel⁸ find antibodies in the

¹ Turban u. Baer: Opsonischer Index und Tuberkulose. Beitr. z. klin. d. Tuberk., 1908, x, 1.

² Löwenstein u. Pickert: Eine neue Methode zur Prüfung der Tuberkulinimmunität. Deutsch. med. Wehnschr., 1908, xxxiv, 2262.

Pickert: Ueber natürliche Tuberkulinresistenz. Deutsch. med. Wehnschr., 1909, xxxv, 1013.

³ Wassermann u. Bruck: Experimentelle Studien über die Wirkung von Tuberkelbacillen-Präparaten auf den tuberkulosekranken Organismus. Deutsch. med. Wehnschr., 1906, xxxii, 449.

⁴ Wolff-Eisner: Frühdiagnose und Tuberkuloseimmunität. Würzburg, 1909, p. 249.

⁵ Czaska: Cit. Sahli: Ueber Tuberkulinbehandlung. Basel, 1910. Dritte Auflage, p. 135.

⁶ Cohn: Ueber komplementbindende Tuberkulose-Antikörper und ihre Beziehungen zur Tuberkulinreaktion. Berl. klin. Wehnschr., 1908, xlv, 1309.

⁷ Weil u. Strauss: Ueber die Rolle der Antikörper bei der Tuberkulinreaktion. Wien. klin. Wehnschr., 1908, xxi, 1058.

⁸ Engel u. Bauer: Ueber die Bedeutung und die Spezifität der komple-

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blood of patients taking large doses of tuberculin, while Neumann and Bauer¹ can establish no relation between the size of the dose and the anti-tuberculin content of the blood. Jochmann² agrees with Bauer and Engel that high doses are necessary to make it manifest, but does not find that the anti-tuberculin necessarily means improvement. Caulfeild³ hopes to show a correlation between clinical progress and serum reactions.

The condition of our present knowledge of antibodies evidently forces us to retreat to a clinical platform for our defence of tuberculin therapy; not because the present knowledge is against tuberculin, but because it is yet too vague to settle anything.

An immunity to subcutaneous doses of tuberculin is in a general way parallel to an immunity to the cutaneous, intracutaneous and conjunctival doses. Pottenger⁴ states that the cutaneous tuberculin test never becomes negative under treatment. Our experience has been that the v. Pirquet test almost invariably becomes negative, as the therapeutic doses of tuberculin become moderately large (e. g., Phipps, No. 2289, at 80 mg. O. T.).

However, that this phenomenon should in itself be used as a guide as to when to resume or to discontinue tuber-

mentbindenden Antikörper bei Tuberkulose und deren Beziehungen zu Heilungsvorgängen. München. med. Wchnschr., 1908, lv, 2273.

¹ Neumann u. Bauer: Cit. Neumann, loc. cit., p. 112.

² Jochmann: Cit. Bandelier u. Roepke, loc. cit., p. 130.

³ Caulfeild: Correlation of clinical progress with the results of immunological studies in pulmonary tuberculosis. Arch. Int. Med., 1911, viii, 440.

Investigations on pulmonary tuberculosis. Jour. Med. Research, 1911, xix, 101.

Preliminary report upon the injection of rabbits with protein-free (Tuberculo-) Antigen and Antigen-Serum mixtures. Proc. Roy. Med. and Chir. Soc., B., 1911, lxxxiv, 390.

Factors in the interpretation of the inhibitive and fixation serum reactions in pulmonary tuberculosis. Ibid., 373.

⁴ Pottenger: Discussion on Pottenger: Some difficulties encountered in the therapeutic use of tuberculin. Jour. Am. Med. Assn., 1911, lvii, 941.

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culin treatment (as is done by Jochmann¹) is unjustifiable. The skin test may become negative while there is no evidence of arrest, or freedom from symptoms, and while the sputum still shows tubercle bacilli. A case in point is that of S. L. Phipps, No. 2289. On December 28, 1907, she showed a + + + v. Pirquet reaction, and sputum with tubercle bacilli. When she had taken 80 mg. of O. T. the v. Pirquet test was entirely negative. This occurred on June 8, 1909. On July 27, 1909, she received 500 mg. O. T., after which no tuberculin was given her. The v. Pirquet test has been administered repeatedly, and has remained negative as late as November 27, 1911—over two years after the cessation of tuberculin. Her sputum, however, still shows tubercle bacilli, and the lesion has slowly progressed, although not virulently.

Koch conceived the healing action of tuberculin to be due to its necrotic effect on tuberculous tissue. He did not claim for it any bactericidal effect, nor is there yet any evidence for such an action. Nor is the unaffected lung tissue immunized. We know that the invasion may extend, even when the patient has had prolonged treatment and has become highly tolerant of tuberculin. The necrotizing effect of tuberculin is no longer held. At present the favorable action of tuberculin is conceived to be due to its immunizing influence and to its focal effects. Löwenstein and Rappoport² spoke strongly for the immunizing effect, contending there is an increased production of antibodies which neutralize the toxins given off by the bacilli or by tuberculous tissue. The laboratory evidence for such immune bodies has been discussed. Clinically the argument for such an antitoxic effect rests upon the remarkable and

¹ Jochmann: Beobachtungen über die spezifische Behandlung der Tuberkulose mit verschiedenen Tuberkulinpräparaten. Deutsch. med. Wchnschr., 1910, xxxvi, 975.

² Löwenstein u. Rappoport: Ueber den Mechanismus der Tuberkulinimmunität. Ztschr. f. Tuberk., 1904, v, 485.

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often early relief from symptoms seen in tuberculin patients in whom there has been no diminution, or even an increase, in the physical signs. Sahli especially assumes that this phenomenon is an evidence of an antitoxic action. Others believe that the increased antibodies are due, not to the direct stimulation of tuberculin, but are secondary to the general improvement following the focal changes. It is impossible to adjudicate the controversy, but we incline to the belief that antibody formation is directly stimulated by tuberculin. Detre¹ is of the opinion that the antibody formation may be detrimental, allowing the existence of a parasitic bacillus, invading further tissue without sufficient resistance on the part of the host. There is no general clinical ground for this belief.

There is no doubt that much, if not all, of the healing effect of tuberculin is due to its focal action. The evidence for such focal changes has been given elsewhere. Some authors, such as Rumpf,² believe that the entire healing effect is due to focal changes following each dose. However, these changes can occur with doses that are too small to elicit a general reaction. As the doses are gradually raised to tolerance the focal changes, mild and healing, continue to occur, and at the same time the immunizing effect of tuberculin, if there be any, may reasonably be expected to manifest itself—after analogy with other specific inoculation.

Bartel and Neumann³ believe that in addition to the focal changes there is a special irritative effect upon the lymphatic system. Gärtner and Römer⁴ have shown an in-

¹ Detre: Diskussionsbemerkung zum Vorträge von Haymans. Wien. klin. Wehnschr., 1908, xxi, 926.

² Rumpf: II Versammlung der Tuberk. Ärzte. Berlin, 1905.

³ Bartel u. Neumann: Lymphocyt und Tuberkelbacillus. Centralbl. f. Bakteriolog., 1906, Abt. I, xl, 518.

⁴ Gärtner u. Römer: Ueber die Einwirkung von Tuberkulin und anderen Bakterienextrakten auf den Lymphstrom. Wien. klin. Wehnschr., 1892, v, 22.

creased lymph flow after tuberculin injections. This increased lymph flow is said to be favorable to healing, on account of the especial effect of lymphocytes on tubercle bacilli—as appears from the work of Bartel.¹ Schulz,² too, finds a lymphocytosis after small doses of tuberculin.

Effect of Tuberculin on the Symptoms.—In determining the effect of tuberculin on individual symptoms, self-delusion is easy. Necessarily, if a patient is improving, he feels better, and the symptoms clear. In fact, as has been said, it is rather the symptoms than the physical signs that clear--and we might strictly end this section here. But it will be well, perhaps, to review briefly the symptoms, to see which ones, if any, are prone to be more influenced—if the patient is capable of improvement.

First, and probably the most striking, is the appearance of a sense of well-being. Many patients spontaneously declare a tonic effect, which we believe exists, though making allowance for suggestion and auto-suggestion.

Weight: The body weight is not particularly influenced. Certainly, if weight alone be a criterion, then superalimentation ranks first, at least for a time.

Fever: Mild pyrexia may be favorably influenced by tuberculin. Indeed, by some tuberculin is spoken of as an antipyretic. This subject will be more fully discussed a little later, and again under Choice of Patients, since fever plays such a large part in determining our choice.

Cough: Cough, especially an irritative, non-productive cough, tends to recede rapidly—but not if it is due to some local condition in the nasopharynx. Such conditions need appropriate treatment. We are not convinced that in the

¹ Bartel: Zur Frage der Infektionswege der Tuberkulose. Internat. Tuberculosis Congress, Washington, 1908, i, 95.

Über Immunisierungsversuche gegen Tuberkulose. Ibid., 188.

² Schulz: Das Blutbild und die Blutreaktion. Beitr. z. klin. d. Tuberk., 1911, xxi, 79.

early period of treatment cough is frequently increased, as stated by Brown and others.

Sputum: Expectoration yields gradually. Where it has been profuse we cannot expect a sudden change. The same is true of the expectoration of tubercle bacilli. These disappear slowly—but more rapidly than without tuberculin. As the quantity of sputum decreases the number of bacilli in the sputum may be relatively increased. Even an absolute increase in the number of bacilli is found by Neumann to be not necessarily an unfavorable sign, as it may be due to an increased exfoliation consequent upon the focal changes. Neumann's dictum, that a sputum-reaction (an increased flow of sputum after a dose of tuberculin) is among the earliest forerunners of a constitutional reaction, is an extreme statement for which there is little ground.

Denys, Pane,¹ Löwenstein,² and Bandelier and Roepke have noted that in tuberculin patients there are more ingested tubercle bacilli in the phagocytes of the sputum, and that these bacilli show regressive changes. Allen³ has not been able to observe such results.

Hemoptysis: We do not know of any specific effect upon hemoptysis, any more than can be expected to accompany healing. Bandelier and Roepke believe that the hyperemia attending the mild focal reactions causes such pressure upon points likely to bleed that hemorrhage is rendered impossible—at least more unlikely than in patients not treated with tuberculin. Brown's statistics, too, show very little incidence of hemoptysis in tuberculin

¹ Pane, cit. De Renzi: Pathogenese, Symptomatologie und Behandlung der Lungenschwindsucht. Wien, 1894.

² Löwenstein: Ueber das Verhalten der Eiterzellen gegenüber den Tuberkelbazillen. Ztschr. f. Hyg. u. Infectiouskrankh., 1906, lv, 429.

Beitrag zur Histologie des tuberkulösen Auswurfes. Ztschr. f. Tuberk., 1907, x, 47.

³ Allen: Phagocytosis, etc., in sputum, as a measure of resistance in tuberculosis. New York Med. Jour., 1907, lxxxvi, 162.

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patients. Whether Bandelier and Roepke's theory is correct or not one thing is certain, tuberculin does not tend to produce hemoptysis.¹

Digestion: The appetite and digestion are decidedly improved, in so far as they are due to the toxemia. Should there, however, be a complicating neurosis, the improvement may be absent, unless the neurosis has been a direct consequence of the tuberculous activity.

Dyspnea: Dyspnea, in so far as it is due to the toxemia and not to emphysema or to much tissue-destruction, is improved.

Pulse: If the tachycardia is proportionate to the weakened systemic condition, it improves correspondingly. If the tachycardia is out of proportion to the general debility, there is presumably an essential defect of the myocardium, and the condition is likely to be protracted, requiring careful regulation of exercise and heart tonics. The blood-pressure is unaffected by single therapeutic doses.

Pains: General, toxic pains tend to clear rapidly as the patient improves. Local thoracic pains, attended probably by pleural fibrosis, have in our experience been stubborn, even when there has been marked improvement in every other way. In fact, we have been unable to relieve rapidly such pains; even in patients with very small lesions, who have been apparently cured for years. Perhaps this is due to scarring.

Complications, such as dry or wet pleurisy, are uncommon in tuberculin patients, although we have seen such pleurisies (both wet and dry) when the patient seemed to be doing excellently in other respects. Bandelier and Roepke emphasize particularly the infrequency of tuberculous complications of all sorts in sanatoria where tuberculin is used. Febrile relapses are particularly uncommon.

¹ Krämer: Tuberkulin u. Hämoptoe. Wien. med. Wchnschr., 1908, lviii, 2139.

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Arneth¹ has noted, according to his system, an improvement in the blood-picture to an extent not seen without tuberculin treatment. This has been confirmed by Uhl,² and others. Anemias improve; the color becomes better, the cheeks rosy. A leucopenia is changed to a leucocytosis. An eosinophilia is also found.³ Hirschfeld⁴ denies any changes due to tuberculin.

As with other therapeutic agents, tuberculin has a better opportunity the earlier the disease. Still, even with the incipients, the results are more lasting if tuberculin has been used. It is particularly for advanced patients that we find tuberculin indispensable. A cure is not to be expected, but cases that otherwise refuse to improve may improve when tuberculin is given them. Not that we can expect a rapidly progressing lesion to halt, but we do mean that patients who have undergone no improvement, or who are even slowly progressive, in spite of the best of care, are often given by tuberculin a shove in the right

¹ Arneth: Die Lungenschwindsucht auf Grundlage klinischer und experimenteller hämatologischer Untersuchungen. Leipzig, 1905.

² Uhl: Ueber die neutrophilen Leukozyten bei der spezifischen Therapie der chronischen Lungentuberkulose. Beitr. z. klin. d. Tuberk., 1906, vi, 248.

³ Franke: Experimentelle Untersuchung über den Einfluss und den Unterschied der Wirkung zwischen dem Menschen und Perlsuchtuberkulin auf das Blut und die blutgildenen Organe der Tiere. Beitr. z. klin. Tuberk., 1908, xi, 351.

Fauconett: Tuberkulöse Prozesse und Lymphozyten. Deutsch. Arch. f. klin. Med., 1904, lxxxii, 167.

Bischoff: Blutuntersuchungen an mit Tuberkulin behandelten Tuberkulösen. Inaug. Dissertation, Berlin, 1891. Cit. Cornet: Die Tuberkulose, Wien, 1907, p. 598.

Rille: Morphologische Veränderungen des Blutes bei Syphilis und einigen Dermatosen. Monatsch. f. prakt. Dermat., 1893, xvi, 188.

Botkin: Hämatologische Untersuchungen bei Tuberkulininjektionen. Deutsch. med. Wehnschr., 1892, xviii, 321.

Sahli: Lehrbuch der klinischen Untersuchungsmethoden. Wien, 1909, p. 913.

⁴ Hirschfeld: Ueber das Verhalten der weissen Blutkörperchen bei kindlicher Tuberkulose. Monatschr. f. Kinderheilk., 1911, x, 38.

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direction. This is not an argument in favor of restricting tuberculin to such desperate patients, but it is to such patients that it is particularly incumbent upon us to give tuberculin.

Pulmonary tuberculosis in children has not been as thoroughly studied as in adults. There is a strongly prevalent belief that in the first year of life especially the prognosis is extremely unfavorable. There has been, too, a prejudice against using tuberculin in young children, on account of a supposed hypersensitiveness in tuberculous children. Ganghofner¹ and Jessler were among the first to advocate the use of tuberculin here. At first the attempts were restricted to glandular and bone tuberculosis, but in recent years the application has been extended to pulmonary lesions. Landgraff, W. Goetsch, Schlossman,² Rohmer and Bauer and Engel³ report favorable results, where the lesions are not large and not very progressive. Heubner and Escherich⁴ find the progressive form hard to treat. Jochmann obtained favorable results with children over three years, but below that age he finds the disease hard to arrest. There is quite a difference of opinion as to the value of extremely large doses, although the work of Hamburger has shown that many children tolerate large doses easily. It may be that the bad prognosis of pulmonary tuberculosis in the first years of life is largely due to the failure to recognize the milder forms, since the diagnosis of respiratory diseases is particularly difficult in the very young.

¹ Ganghofner: Mittheilung über das Koch'sche Heilverfahren aus dem Kaiser Franz Josef-Kinderspital in Prag. I Bericht der pädiatrischen Klinik. Prag. med. Wehnschr., 1891, xvi, 31.

² Schlossmann: Ueber die therapeutische Verwendung des Tuberkulins bei der Tuberkulose der Säuglinge und Kinder. Deutsch. med. Wehnschr., 1909, xxxv, 289.

³ Engel: Ueber das Verhalten der kindlichen Tuberkulose gegen Tuberkulin. Beitr. z. klin. d. Tuberk., 1909, xiii, 245.

⁴ Escherich: Wien. med. Wehnschr., 1912, No. 1.

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Excellent results with tuberculin are seen also in children who have been exposed to infection in their homes, whose physical signs are negative, but who are pale and weak, and who give positive cutaneous or conjunctival reactions. Such children probably have tuberculous glands concealed somewhere. At any rate, they do splendidly under the treatment, which may be here looked upon as partly prophylactic.

Hammer, Hawes and Floyd, Wilkinson,¹ Hamman and Wolman,² and others³ have had good results in administering tuberculin to ambulant patients. In spite of the fact that such patients are not well controlled from the point of view of exercise, hygiene and diet, and that not infrequently even mildly febrile patients have to make the semi-weekly trips to the clinic, the dispensary tuberculin treatment has saved many sanatorium graduates from relapses, even while at work, and has allowed others to remain at work uninterruptedly without previous sanatorium treatment. Our experience demonstrates that with fairly intelligent patients tuberculin can be given safely, even in a dispensary, where the control is necessarily far

¹ Wilkinson: Tuberculin Dispensaries—A reply. *Brit. Med. Jour.*, 1911, 418.

² Hamman and Wolman: Tuberculin treatment among dispensary patients. *Johns Hopkins Hosp. Bull.*, 1909, xx, 225.

³ Blümel: Die Notwendigkeit und Möglichkeit ambulanter Tuberkulinbehandlung durch den praktischen Arzt. *Med. Klin.*, 1911, vii, 405.

Shively: Tuberculin therapy in clinic and office practice. *Interstate Med. Jour.*, 1911, xviii, 747.

Pringle: Tuberculin Dispensaries. *Brit. Med. Jour.*, 1911, i, 297.

Lamb: Tuberkulindiagnostik und ambulatorische Tuberkulinbehandlung. *Wien. klin. Wchnschr.*, 1911, xxiv, 10.

Merriman: Reports of cases treated with tuberculin. *St. Luke's Hosp. Reports*, 1910, ii, 249.

Miller: The tuberculin treatment of pulmonary tuberculosis in office and dispensary practice. *Tr. Am. Climatological Assn.*, 1910, xxvi, 166.

Fraser: Tuberculin dispensaries and sanatoria. *Clin. Jour. (London)*, 1910, xxxvii, 149.

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less than that exercised in sanatoria, and probably less than that which an intelligent practitioner has over his private patients. Ulrici¹ speaks rather unfavorably of the tuberculin treatment of ambulant patients.

Results in Tuberculous Laryngitis.—Since the action of tuberculin is specific, there is no reason for not employing it in the treatment of tuberculosis in any organ. Indeed, *a priori*, and empirically, the only contraindication against its use for any situation is the consideration of the harmful results following upon a focal reaction. Since a strong reaction can be avoided, there is no reason for not using tuberculin against tuberculosis anywhere in the body. Next to the lungs, the larynx has been most frequently treated, since pulmonologists have been those most interested in tuberculin. An advantage in the treatment of the larynx is the visibility of the organ, which permits a control of the reaction. The disadvantage is that, tuberculous laryngitis being secondary to pulmonary tuberculosis, our treatment of the larynx is regulated, not by the dose the larynx needs, but by the dose the lungs will tolerate. It also frequently happens that the lung condition is not recognized, or is neglected by the laryngologist, so that the treatment is not as successful as it might be. There is danger of edema of the larynx from a violent reaction (Thorner), but this need not occur with modern methods.

C. Gerhardt and B. Fraenkel were among the first to use tuberculin in laryngitis, and met with such success that they persisted in using it. Krause, Schroeder, Wilkinson,² Sahli, Bandelier and Roepke have all reported good results—better than without tuberculin. The course of the disease is much more favorable than by merely local and

¹ Ulrici: Zur Frage der ambulanten Anwendung des Tuberkulins. Med. Klin., 1911, vii, 1693.

² Wilkinson: Tuberculin in laryngeal tuberculosis. Brit. Med. Jour., 1910, 1705.

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general treatment. Initial reddenings and moderate infiltrations usually resolve smoothly, and even small ulcerations may heal. Where softening of an infiltration has already occurred, the inevitable ulceration is likely to heal, if not too large. In the case of some large infiltrations that did not yield to local treatment regression occurred under tuberculin.

The larger infiltrations, fissures and ulcers and deep changes extending into the perichondrium need radical local treatment in addition to the tuberculin. But Grant and Watson-Williams¹ speak strongly of tuberculin as an anodyne here. Of course the pulmonary condition affects the prognosis. Too much emphasis cannot be laid upon the necessity of treating the patient as well as the larynx. Bandelier and Roepke state that they have seen no new tuberculous laryngitis develop in patients that are treated by tuberculin, even where the pulmonary condition is advanced. We do not know that this is generally true, but it is true that the complication occurs with comparative rarity in tuberculin patients.

Results in Tuberculous Adenitis.—In the realm of surgical tuberculosis, tuberculin has been most frequently applied to the treatment of tuberculous lymph-glands, both in adults and children. Best fitted for treatment are those glands which have not yet softened. Where softening or fistula is already present surgical measures are necessary, but these need not be as extensive as when tuberculin is not to be used subsequently. Where the softened area is small aspiration by puncture may be sufficient. Krämer early pointed out the advantages of combining tuberculin with surgical treatment where the latter is inevitable. Since then the application of tuberculin to the therapy of adenitis has become almost popular. On account of the

¹ Grant and Watson-Williams: The treatment of tuberculosis of the larynx. *Brit. Med. Jour.*, 1911, 1001.

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fairly exposed position of the focus the reaction can be easily watched, and the size of the dose easily guided. The prognosis is much better than in laryngitis, because fewer of the gland-cases are complicated by active pulmonary disease. The results achieved in this branch of tuberculin therapy have been most encouraging. Many authors speak warmly of the manifest improvement under treatment. Petruschky, in patients with still closed glands, gets 100 per cent. of healing. Bauer and Engel have never seen softening after the treatment has been begun. Pogue had extremely good results even in cases with fistulæ. Jochmann obtained results that he found unattainable without tuberculin. Bandelier and Roepke found excision rarely necessary. Rohmer had the opportunity of seeing fibrous encapsulation of treated glands at autopsies of three children under two years, dying of other complicating diseases. Other favorable results are reported by Sahli, Heubner, Baginsky, Wright, F. Krause, Peiper, Scherer, Dumas, Arondale, Ullman, Raw, Pottenger, Hawes, Neumann, Ager,¹ Stoll,² Philip,³ Griswold⁴ and others. Waugh,⁵ however, does well to remind us that many non-tuberculous glands have no doubt been treated with tuberculin.

Dautwiz⁶ made an especial study of tuberculosis of the intrathoracic glands. By tuberculin he obtained more recoveries and more lasting results than by ordinary treatment. His radiographic plates show, during the later stage

¹ Ager: The therapeutic use of tuberculin in intrathoracic tuberculosis of children. *Am. Jour. Obst.*, 1911, lxiii, 368.

² Stoll: The diagnosis of tuberculosis of the bronchial glands. *Am. Jour. Med. Sc.*, 1911, cxli, 83.

³ Philip: The tuberculous gland. Its significance and treatment. *Lancet*, 1910, ii, 19.

⁴ Griswold: Tuberculosis of the cervical lymph glands. *Northwest Med.*, 1911, iii, 189.

⁵ Waugh: The use of tuberculin in so-called "tuberculous" glands. *Quart. Jour. Med.*, 1911, iv, 521.

⁶ Dautwiz: *Beiheft z. med. Klin.*, 1908, Ht. 9.

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of treatment, a better defined shadow of the involved glands—which he interprets as an evidence of encapsulation. v. Starck, too, saw improvement, subjective and objective, in tuberculosis of the bronchial glands. Reunert produced regression in a case of generalized tuberculosis of the lymphatic system, resembling pseudoleukemia. We ourselves have had good results in treating both closed and open glands. We have obtained recovery, for at least three years, in a child of six months, with numerous glands involved and broken down. In the open cases discharge soon stops, the scar becomes pale and elastic. Negative reports are few. Guinard never saw anything but softening and liquefaction. His experience is uniquely unfortunate.

Results in Tuberculosis of the Eye.—No greater tuberculin enthusiasts can be found than among the ophthalmologists. In the treatment both of grave and minor lesions most fortunate and surprising results have been obtained. Lesions in every part of the eye have been noted to undergo great and permanent improvement. Vision has been restored where it has been seriously interfered with, and eyes have been saved which had already been destined to enucleation. Among the lesions successfully treated are tuberculous keratitis, scleritis, and episcleritis, tuberculosis of the conjunctiva, iris, ciliary body, choroid, retina, hyalin body and optic nerve. A host of names could be quoted, among them v. Hippel,¹ Davids,² Scheuermann,³ Schoeler,⁴ Cramer, Augstein, Harnicker, Weeks. The focus of the

¹v. Hippel: Ueber den Nutzen des Tuberkulins bei der Tuberkulose des Auges. Arch. f. Ophth., 1904, lix, 1.

²Davids: Ueber den Nutzen des Neu-Tuberkulins (Bacillenemulsion) bei der Tuberkulose des Auges. v. Graef's Arch. f. Ophth., 1909, lxix, 231.

³Scheuermann: Ueber einen Fall von Solitartuberkel der Netzhaut, Aderhaut, und des Sehnervenkopfes, geheilt mit Neu-Tuberkulin-Bazillen-Emulsion. Ztschr. f. Augenheilkund., 1909, xxii, 37.

⁴Schoeler: Klin. Jahrb., 1909, xxii.

disease being visible there is little difficulty in dosage. Reactions, except the very mildest, should be avoided, for fear of ulceration. The vascular tissue of the iris and ciliary body is especially prone to heal, and Augstein and Cramer have reported the cure of desperate conditions in this locality. Diem and Stock, Schoeler, Cramer and others speak with enthusiasm of the treatment of tuberculous choroiditis. Augstein and Tardieu report successful treatment with tuberculin when other measures had completely failed. v. Hippel thinks ophthalmologists especially should be grateful to Koch for his tuberculin. Scheuermann reports restoration of sight in a case of solitary tubercle, involving the retina and optic nerve, which at first looked as if it would surely destroy the eye. Pick reports a cure of an extensive lesion involving the superficial and deep parts of the bulb. We ourselves have seen uniformly good results in those cases of tuberculous keratitis and iritis which have come under our notice. Photophobia rapidly disappears, and vision is gradually restored, unless tissue destruction has occurred before treatment. From the evidence before us it would seem incumbent upon ophthalmologists to avail themselves of the specific aid of tuberculin.

Results in Tuberculosis of the Bones and Joints.—In bone and joint tuberculosis, as in glandular tuberculosis, there is a growing opinion that surgery may be prevented or supplemented by tuberculin. The latter is regarded by Krämer as an indispensable element of the after-treatment. Schlossmann and Engel report a series of cures in children, attested by X-ray plates. Complete anatomical healing occurred in a case of Spina Ventosa, in a tuberculous knee-joint and in a tuberculosis of the ulna that had progressed to abscess formation. Deterding and de Groot cured a typical spinal caries. Lenzmann¹ has seen rapid

¹ Lenzmann: Beiheft z. Med. Klin., 1909, Ht. 2.

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improvement in sluggish fistulæ, in which other measures had been of no avail. Jochmann has seen very good results in bones and joints, but he especially commends tuberculin as an after-treatment in those cases in which surgical measures were inevitable. This is in order to influence favorably the infected neighboring tissue and glands. Bandelier and Roepke have favorable reports. They find that operative wounds heal with unusual rapidity under tuberculin. Brunzlow reports a case of tuberculosis of the knee-joint which refused to heal in spite of incision and drainage, iodoform-glycerin injections and Bier's hyperemia. Under tuberculin there was complete healing with restoration of function. Other favorable reports are from Power, Raw, Neumann, Sonnenburg, Ullmann, Lüdke, Aronade, Pogue, Meadowikow, Klose,¹ Seyberts,² Beasley,³ Jones, Smith and Cathcart.

Results in Tuberculosis of the Genitourinary System.

—The prognosis depends largely on the accompanying pulmonary condition and on the extent of the local process. General hygienic measures are indispensable. There is widely extended recognition of the value of tuberculin as an adjuvant, but discussion rages as to when and what extent surgical interference is advisable. Especially uncertain is this in renal tuberculosis. Israel recognizes tuberculin as a valuable remedy in renal tuberculosis, but advises extirpation of the kidney when only one kidney is involved, and the bladder is still unaffected. Knorr takes the same view. They recommend tuberculin treatment when both kidneys are affected, either as a substitute for

¹ Klose: Ueber die moderne orthopädische Behandlung der Gelenktuberkulosen. *Med. Klin.*, 1911, vii, 801.

² Seyberts: Beitrag zur Behandlung der örtlichen Tuberkulose mit Tuberkulin Rosenbach. *Beitr. z. klin. Chir.*, 1911, lxxiv, 744.

³ Beasley: Local use of tuberculin in the treatment of open or surface forms of tuberculosis. *Jour. Indiana Med. Assn.*, 1911, iv, 432.

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or as an accompaniment of surgical procedure. Karo,¹ too, favors extirpation if only one kidney is affected. Casper² speaks for the extirpation of the one infected kidney, even if the process seems extensive. All of them, however, recommend post-operative treatment with tuberculin. Douglas³ and Pedersen⁴ also report good results in renal cases. Whiteside⁵ and Bachrach and Necker⁶ restrict the use of tuberculin to very early cases. Bevan⁷ and Kümmell⁸ are only mildly favorable to tuberculin, and others have seen no good results.⁹ Good results in bladder tuberculosis are reported by Schulze, Jochmann, Lenhartz, Pogue, Pardoe,¹⁰ Schroeder, Sahli. Jochmann, Lenzmann, Ullmann, Pogue, Kehl have treated successfully tuberculosis of the testicle, epididymis, and prostate gland. Birnbaum¹¹ has had striking success in the treatment of tuber-

¹ Karo: Beiträge zur spezifischen Behandlung der Nieren-und Blasentuberkulose. Tuberculosis, 1909, viii, 513.

Weitere Erfahrungen über die spezifische Therapie der Nierentuberkulose. Med. Klin., 1911, vii, 1005.

² Casper: Die Diagnose und Therapie der Blasen-und Nierentuberkulose. Berl. klin. Wehnschr., 1909, xli, 1005.

³ Douglas: Tuberculosis of the urinary tract. Med. Press and Circular, London, 1911, xcii, 550.

⁴ Pedersen: Two cases of renovesical tuberculosis treated with the bacillus emulsion. New York Med. Jour., 1911, xciii, 371.

⁵ Whiteside: Renal tuberculosis. California State Jour. Med., 1911, ix, 16.

⁶ Bachrach u. Necker: Zur Tuberkulinbehandlung der Urogenitaltuberkulose. Wien. klin. Wehnschr., 1911, xxiv, 1363.

⁷ Bevan: Tuberculosis of the kidney and ureter. Surg. Gynec. and Obst., 1911, xii, 324.

⁸ Kümmell: Die operative und spezifische Behandlung der Nieren-und Blasentuberkulose. Therap. d. Gegenw., 1910, li, 540.

The operative and specific treatment of renal and vesical tuberculosis. Surg. Gynec. and Obst., 1911, xii, 311.

⁹ Frank: Ueber Nierentuberkulose. Centralbl. f. Grenzgeb. d. Med. u. Chir., 1911, xiv, 249.

¹⁰ Pardoe: The treatment of tuberculosis of the urinary system by tuberculin (T. R.). Lancet, 1905, ii, 1766.

¹¹ Birnbaum: Das kochsche Tuberkulin in der Gynäkologie und Geburtshilfe. Berlin, 1907.

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culosis of the female adnexa, even with peritonitis. He no longer performs laparotomy in such cases, but gives tuberculin instead. Prochownik,¹ too, reports fine results in tuberculosis of the female genitalia, and Kolischer² speaks favorably of tuberculin here. According to Graefenberg, dysmenorrhea due to tuberculous toxins can be relieved by tuberculin.

No doubt surgical intervention is unfavorable in many instances. But it has become more and more the feeling of surgeons that general supporting measures are not sufficiently tried before operation is deemed necessary. Halsted, in this country, has been one of the earliest to insist upon this view in the treatment of surgical tuberculosis. And it should be remembered that among supporting and stimulating measures tuberculin takes a high rank.

Results in Tuberculosis of the Skin.—Lupus is notoriously stubborn, in spite of the numerous therapeutic measures that have been devised. From a very early period tuberculin has been used. Koch himself reported success with tuberculin, and so have many writers since then. It would seem, however, from a general view of the evidence, that many cases refuse to heal even with tuberculin, and it is, therefore, necessary for the treatment to include all known remedies and devices. Tuberculin is especially indicated where the process is deep or involves the mucous membranes, so that excision or curettage is difficult. But there is no reason why the aid of tuberculin should not be sought even in mild cases. Favorable reports are at hand from Adler, Beck, Brocq, Heermann, Leredde, Sahli, Wright, A. Neisser, Blachko, Heuck. Senger recommends locally a 3-to-10-per-cent. tuberculin salve where there is

¹ Prochownik: Die weibliche Genitaltuberkulose vom klinischen Standpunkte. München. med. Wehnschr., 1909, lvi, 1046.

² Kolischer: Tuberculosis of the tubes, ovaries, and bladder. Surg. Gynec. and Obst., 1911, xii, 341.

ulceration, combined with the Roentgen ray. The focal reactions form a convenient guide to the dosage. Where excision is necessary the focal reactions, by demarking the active tissue from the inactive, indicate the amount to be removed.

We ourselves have seen an excellent result in a case of deep tuberculosis cutis. Of course the good effect of tuberculin upon the general condition is not to be forgotten.

Results in Tuberculosis of the Serous Membranes.—The treatment of pleurisy is, of course, most frequently concomitant with that of the lungs. Pleural pains due to proliferative pleurisy without striking lung changes may be favorably influenced. Effusion has been known to occur even while the patient's pulmonary condition is improving, and the tolerance to tuberculin has been good.

Olshausen, Zweifel, Fritsch, Ganghofner and Raw have successfully treated tuberculous peritonitis, often without laparotomy. Birnbaum is especially pleased with his results in this form of tuberculosis. He has seen cures both in the plastic form and in cases with ascites.

Results in Tuberculosis of the Ear.—Otitis media of a tuberculous nature is a field for treatment with tuberculin, but the affection is usually resistant. Cipes¹ reports a cure of a double otitis media.

Results in Tuberculous Arthritis of Poncet.—Poncet² has described a tuberculous arthritis simulating rheumatic fever and due to toxins. We have had occasion to treat a woman with a small lung lesion, who suffered greatly, however, from fleeting multiple arthritis. Under even moderate doses of tuberculin the arthritic phenomena have disappeared.

¹ Cipes: Tuberculosis of both ears cured by tuberculin. *New York Med. Jour.*, 1911, xciv, 835.

² Poncet et Leriche: Rhumatisme tuberculeux ankylosant. *Bull. de l'acad. de méd., Paris*, 1904, lii, 250.

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Results in Tuberculosis of the Intestines.—Tuberculosis of the intestines, whether ulcers or indurations, is susceptible of treatment. We have had occasion to treat a patient with tuberculosis of the cecum, discovered during an appendectomy. The man had been subject to frequent acute abdominal attacks which were not relieved by the appendectomy, but which disappeared rapidly and permanently under tuberculin.

Results in Tuberculous Meningitis.—Vernet¹ claims to have cured one case of tuberculous meningitis, and Maurange² saw improvement in one case. Neumann well suggests that frequent lumbar puncture be associated with the tuberculin therapy, in order to prevent death from intracranial pressure, and thus afford the tuberculin an opportunity to exert its influence.

Results with the Different Tuberculins.—The results obtained with tuberculin in the treatment of pulmonary tuberculosis and of tuberculosis in other organs, as reported above, have been obtained by various tuberculins. Those that have been most frequently mentioned in the various reports are Koch's O. T., T. R. and B. E.; Béranek's Tuberculin, Denys' B. F., Jochmann's protein-free tuberculin and the bovine tuberculins. In order to see whether in the treatment of any one form of tuberculosis better results were obtained with a particular variety of tuberculin, we tabulated for each organ the choice tuberculin as it seemed to each author. We found that for all the organs the list is practically the same. For example, in the literature on the treatment of glands, one of the following tuberculins is regarded by some author as the most suitable for the treatment of glandular tuberculosis:

¹ Vernet: Un cas de méningite tuberculeuse traité par la tuberculine Béranek. Rev. méd. de la Suisse Romande, 1907, vii, 562.

² Maurange: De la tuberculine dans la méningite tuberculeuse. Semaine méd., 1896, 448.

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Koch's O. T., T. R. or B. E., Bérameck's tuberculin, Denys' B. F., Jochmann's protein-free tuberculin Endotin. Now and again some other tuberculin is mentioned, but the three tuberculins of Koch, Denys' and Bérameck's tuberculins, with recently the protein-free preparations, are by far the most used. However the individual preferences of authors may differ, frequently mention is made, as by Bandelier and Roepke, or by Jochmann, that he was able to obtain good results with any of the above tuberculins. We cannot, from a review of the literature, see that there is, at present, any clinical basis for preferring any one of the principal tuberculins over another.¹ Preferences are often based on a worker's long-continued use of a special brand, and his consequent unwillingness to change. However, some writers feel that there is a demonstrable difference in the action of some of the chief tuberculins. For example, although Bandelier and Roepke think them all therapeutically efficient, they believe that O. T. causes more inflammatory changes at the focus, and that B. E. is more apt to give fever reactions than focal changes. But they prefer B. E. as an antipyretic over O. T., when fever is already present. Brown has also noted fever reactions with B. E., unaccompanied by other symptoms. Kehl thinks O. T. an efficient antipyretic, while Neumann prefers T. R. or B. E., as does F. Krause. However, Denys' B. F. and Bérameck's tuberculin have strong defenders of their antipyretic action. Bandelier and Roepke think T. R. or B. E. produces more anti-bacterial immunity than O. T., and yet Goetsch² had to change from T. R. to O. T. in order to cause disappearance of the bacilli from the sputum. Work

¹ Wolff-Eisen: Theoretische Grundlagen und praktische Ergebnisse der spezifischen Tuberkulosetherapie. Berl. klin. Wehnschr., 1911, xlviii, 1286.

Blümel: Die Wahl unter den verschiedenen Tuberkulinen. München. med. Wehnschr., 1911, lviii, 1822.

² Goetsch: Ueber die Behandlung der Lungentuberkulose mit Tuberkulin. Deutsch. med. Wehnschr., 1901, xxvii, 405.

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with agglutinins does not bring us any nearer to a reasonable choice, since the weight-relation of the various brands has been so often disregarded. As for the protein-free preparations, Jochmann well says that, while they are somewhat less apt to cause fever than the others, the therapeutic effect is about the same. In other words, while the tuberculins grown on protein media contain small amounts of non-specific pyrogenic substances, these are not enough to hinder the therapy, and, furthermore, only infrequently is the fever due to the non-specific rather than to the specific components.

Koch believed in the existence of a human and bovine type of the tubercle bacillus, but he did not affirm a difference in the tuberculins derived from the two types. C. Spengler, however, believed that the tuberculins from the two types act differently. His experiments consisted in determining, from a study of the sputum, the type of infection, and in then treating some of the patients with an isotoxic tuberculin (derived from their own type of bacillus), and others with an allotoxic tuberculin (derived from the other type). He concluded that higher agglutinin values, and more lasting agglutinins, could be obtained by fewer doses of tuberculin, and with less fever production, when the allotoxic tuberculin is used. Bandelier and Roepke could not confirm his work. Spengler's clinical application of his theories is that patients should be treated with an allotoxic tuberculin, at least in the beginning. The type of infection, he asserts, can be determined from the sputum, but, since this is difficult,¹ he recommends Detre's differential

¹Spengler distinguishes in the sputum two types of the tubercle bacillus, the *Humanus brevis* and the *Humano-bovinus* or *Humano-longus*. He devised two stains for the differentiation of these types, the Picric Acid method and the Capsule method. Bonome (*Präzipitin-Reaktion als diagnostisches Mittel der Tuberkulose und zur Differenzierung zwischen Menschen- und Rindertuberkulose. Centralbl. f. Bakteriologie, Abt. I, 1907, xliii, 391*) has confirmed by biological tests the existence of two such types, but there is lack of agree-

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cutaneous reaction. Others who like to use bovine tuberculins are Nathan Raw,¹ Pottenger, Brauns,² Hollós,³ Wolff.⁴ Some of the authors who recommended bovine tuberculins do not determine the type of infection, but assume that as a rule bones and glands are infected by the bovine type and lungs by the human type, and then proceed to the use of the allotoxic tuberculin. Bandelier and Roepke tried Koch's bovine tuberculin in 300 cases. The results were not better than with human tuberculins. It seemed to them that the bovine is simply a milder tuberculin. Judging from the skin reactions, we came to the same conclusion. In fact, this quantitative difference is not only the essential difference between the bovine and human tuberculins, but also between the leading varieties of the human tuberculins. They all produce the characteristically specific reaction; they all immunize reciprocally against each other, as can be shown by the subcutaneous, the cutaneous or the conjunctival test. They all produce good results in all forms of tuberculosis. No doubt there are minor differences, many of which depend upon non-specific elements, but these minor differences do not prevent the successful and innocuous use of any of these tuberculins. Judged by the ease of injection, the more soluble forms are to be preferred over suspensions, since the latter cause

ment as regards the value of Spengler's stains in the differentiation of these types.

¹Raw: Human and bovine tuberculosis with especial reference to treatment by different kinds of tuberculin. *Brit. Med. Jour.*, 1911, ii, 1082.

The treatment of pulmonary tuberculosis with bovine tuberculin. *Lancet*, 1911, i, 927.

²Brauns: Die Grundprinzipien des Carl Spenglereschen Tuberkulose-Schutz-und Heilimpfverfahrens. IV Versammi. der Tuberk. Aerzte, Berlin, 1907, 202.

³Hollós: Ungarische Chirurg. Jahresbericht, 1908.

⁴Wolff: Tuberkulinbehandlung, insbesondere Perlsucht-therapie, nach Karl Spengler (Davos). *Wien. med. Wehnschr.*, 1907, lvii, 2515.

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more local trouble by remaining in the depot and being irregularly absorbed, thus producing cumulative effects. Perhaps the more frequent fever reactions of B. E. are due to such factors, which would be one objection to B. E., as also is the greater tendency to local infiltration, which interferes with the detection of a real local reaction. We are inclined to the use of a soluble preparation, such as B. F. It is possible that idiosyncrasies to unknown components make a change in the kind of tuberculin advisable in certain patients, but only rarely is it necessary. Logically, an unheated tuberculin derived from a protein-free medium is most to be preferred, in the light of present knowledge. But such tuberculins have, up to now, not been used as extensively as the rest. Brown prefers B. E. in B. F., seeking, perhaps, to get bacteriolytic as well as anti-toxic immunity. Immunity experiments, however, do not justify a classification of tuberculins on such grounds. The immunity obtained by all seems to be of the same kind.

The negative evidence as regards the effect of tuberculin on pulmonary tuberculosis consists of two kinds. First, that of authors who criticize tuberculin on a priori grounds, or because of the illogical basis of some of the favorable reports. The second group consists of authors who have used tuberculin and have not been satisfied with the results. We know of no workers dealing with a large number of patients who have seen no good results, unless the cases were all far advanced and progressive. The reports of small numbers of cases need not be cited, as the classification is open to the objections discussed in connection with the favorable reports. We can only repeat that of the people who have used tuberculin the great bulk feel that it is a decidedly useful agent in the treatment of tuberculosis. As for statistics, based on life-duration and on sputum, we know of none that are unfavorable, where

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the treated and the untreated have been fairly selected and apportioned.

More valuable than the haphazard and negative reports has been the criticism of such men as Köhler, Meissen¹ and Shaw.² The former, particularly, have, by their virile attacks, prevented an overrating of tuberculin therapy. It is due to them, in a large measure, that reports dealing almost entirely with dubious incipient cases became ludicrous. Köhler well points out that the only incontestable basis of an estimation of the results are the life-duration statistics, and we heartily agree with him. He should have added, however, that sputum statistics are the next valuable, and will remain highly important until some years hence.

With one dictum of Köhler we cannot agree—namely, that the value of tuberculin must be attested, at present, only by the sudden arrest by tuberculin of a progressive, advanced case that has continued to progress under the ordinary hygienic-dietetic treatment. While such arrests do occur (e. g., Neumann's case), still we can conceive of a drug being useful, even if not submitting to such an extreme test. A drug that affects the life statistics and the sputum statistics favorably cannot be denied a claim to usefulness.

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The ultimate object of giving tuberculin therapeutically is, of course, to heal a tuberculous lesion. Except for a very few who, like Klebs, believe that the tuberculin has a direct bactericidal effect upon the noxious agent, the tubercle bacillus, the modern mode of expression would be that

¹ Meissen: Betrachtungen über Tuberkulin. Ztschr. f. Tuberk., 1907, x, 285.

² Shaw: The present position of the vaccine treatment of pulmonary tuberculosis. Practitioner, London, 1910, lxxxv, 744.

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tuberculin is given in order to heal, by its focal effects, and in order, in some way, to increase the immunity of the body against the bacillus or its poisons. Whether this immunity is simple or complex, and exactly what it is, may not be definitely in the minds of the workers, but the present tendency of medicine leads almost every one to this natural method of expression. Certainly, nothing is known to induce one to believe that tuberculin acts like an anti-toxin or even like a chemical bactericide, such as salvarsan. Immunity in some form it must give, if it is to be of any avail. To resume briefly what has been dealt with in the First Section of this book, pages 23, 52, the immunity against tuberculosis is by some supposed to consist in a bacteriolytic and an antitoxic factor. It has not been settled whether tuberculin produces one or the other, and, if both, to what degree. The claims differ for the various tuberculins, but it has been pointed out that the kind of immunity attained by all is very much the same, and that it apparently does not result directly in a bactericidal effect. As regards the manner in which the attainment of immunity can be judged, the clinical standard is, of course, complete or partial recovery, freedom from relapse and a resistance to new infections. More subtly the immunity is generally judged by the decrease of sensitiveness to doses of tuberculin previously inducing a reaction in a constitutional local or focal manner—by local, of course, including the stich-, the cuti-, and the conjunctival reaction. In animals the immunity may be further tested by the refractoriness of the animal to reinoculation with living bacilli; and in both human being and animals antituberculin, agglutinins or opsonins may be sought.

In spite of all the technical claims and assertions, when we come to the use of tuberculin therapeutically, we must hold fast to the fact that we do not as yet know either tuberculin or its mode of action, nor indeed what the fac-

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tors of immunity are. The advocates of the use of tuberculin must abide solely by the clinical results. If we are satisfied with the results we will use tuberculin, whatever we think of the theories as to its mode of action; and, on the contrary, no intrinsic harmony of the theories will force us to use tuberculin, if the results do not please us.

Although logically the route by which the drug is administered should be considered before the questions of dose and interval, yet, on account of the almost exclusive employment of the subcutaneous route, we shall describe the dose and time for that route before discussing the other modes of administration. The subjects that immediately present themselves are: The initial dose, the maximum dose, the interval between doses and the duration of treatment. However, on account of facts which will soon be unfolded, it is best to avoid such a speciously logical discussion and to view the problem from an altogether other aspect. For we shall find that, whether it be definitely stated or merely implied, all questions as regards dose and time have had the answers to them determined almost solely by the attitude of the writer toward the tuberculin reaction. In brief, the therapist dealing with tuberculin must know once for all whether he does or does not wish to obtain symptoms of a tuberculin reaction during the treatment. For the size of the dose will depend upon his desire to obtain a reaction, or upon his anxiety to avoid it.

The Desirable Attitude Toward Reactions.—It will be instructive to inquire into the history of the attitude of phthisiotherapists upon this critical matter. Koch administered a dose large enough to elicit a strong constitutional and focal reaction and at intervals of one or more days repeated the dose until that dose no longer produced a reaction, whereupon a still larger dose was given—one large enough to produce a reaction—and the former procedure repeated. Cures were said to be accomplished within

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the course, not of months, but of weeks. Of course, the idea propelling Koch was that the inflammatory focal changes occurring during the reaction resulted in a scarring and healing, such as he had witnessed in lupus. To him the administration of a dose of tuberculin was futile if it did not produce a frank constitutional reaction and its usual focal accompaniments. The size of the dose was regulated by this aim. Reactions caused beneficent inflammatory changes, and to obtain these reactions the tuberculin is used. The effect of each dose had to be made evident and palpable to this pioneer of tuberculin therapy. If no clinical spectacle followed upon a dose of tuberculin he inferred that he had been too cautious, and at once took a great stride, so as to compensate for his previous slowness. He reported cures. Others reported deaths, numerous deaths. He retorted that their patients were too sick for treatment, their lesions were too far advanced for them to submit to this inflammatory therapeutic ordeal without danger of acute exacerbation and a hastened exitus. Only those not severely tainted by the infection he thought fit to pass through this therapeutic furnace unsinged. His retort was in all probability correct, in so far as he accused others of using patients with advanced and progressive lesions. However, we at this date know of no patients, however incipient the tuberculous disease, to whom we could predict and assure a safe journey through such a reactionful therapeutic (?) course. No doubt some patients could not be palpably harmed by the ordeal, a few indeed (from what we know of the pathology) would have the cure hastened, but the fact to remember is that we have no means of sifting the few from the many, and that many more would be injured, and grievously, by such a cure. In fact, the results obtained led to the sad period known as the "tuberculin delirium"—and to the consequent downfall of the arrogant therapy to an humble posi-

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tion, whence it is but just emerging, chastened and refined, to assert its modest, but now truthful, claims to a therapy less spectacular but more healing; less forceful but more gently persuasive; healing a few, helping many, and hurting none.

At the present time tuberculin is nowhere used with the frank desire of obtaining strong reactions. All are in unison upon the advisability of avoiding such reactions, not because they harm all cases, but because the size of a reaction cannot be controlled, and it may unexpectedly surge out of the bounds of beneficent action. Yet, in spite of the unanimity of the fear of large reactions, the tuberculin therapists may still be divided into two camps—the timid and the courageous. The timid camp is so much afraid of reactions that it strains every energy to detect the earliest signs of approaching sensibility. It does not wait for a general reaction to prevent the increase of a dose, but it interprets in a cautious manner every constitutional symptom, slight rise of temperature and mild local reaction, as a warning signal. The other camp is bolder—it is willing to come within fair sight of danger if not actually to court it. The bold therapists of this group do not refrain from raising the dose at the least symptoms of a reaction. They rise boldly until there is definite evidence of an oncoming reaction. We might say that at heart this group thinks mild reactions favorable, but cannot aim for them directly, since they may obtain much more than they desire. But, by being bold, they do succeed in eliciting a considerable number of moderate reactions and, it must be said, some quite strong ones.

The leading exponents of the timid group are Trudeau and Sahli. The latter, in an excellent monograph, sums up the hopes and fears of his teachers and followers. Petruschky is a fair example of the opposing group. Banderliet and Roepke occupy a somewhat intermediate posi-

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tion. While each writer marshals many facts, it is fair enough to state that Sahli's chief contention is that, the size of a reaction not being controllable, it is first of all essential to do no harm. His clinical experience leads him to think that cases treated cautiously, and that have experienced no reactions, attain a tolerance for high doses as soon as, and even sooner than, those that are rushed. Bandelier and Roepke have found, too, that high agglutinin values are reached by patients that have had no reactions during treatment. Petruschky believes that by proceeding very cautiously much time is wasted and there is not produced enough focal reaction to promote healing.

Whether mild reactions are or are not to be avoided has not been definitely settled. Certainly strong ones are discountenanced. The attitude toward mild reactions is perhaps a matter of temperament. We ourselves believe that good results are obtained by the slower method, and with less risk.

With this difference between the two methods kept in mind, we shall now present a scheme of dosage and interval which will lend itself, according to the inclination of the worker, to either Sahli's or Petruschky's method. It is largely the scheme that has been followed at the Phipps Dispensary, with modifications from time to time. Indeed, "scheme" is too hard a word to apply to a set of rules or suggestions as to the most advisable way to proceed. We say this because, especially in using tuberculin, it is necessary to study the individual patient rather than the scheme, in order to say when and what the next dose shall be. In other words, no matter what scheme of dosage any particular clinic may be theoretically attached to, it is safe to assume that in the case of very few patients will that scheme be consistently adhered to over any considerable length of time. For example, we believe that in order to avoid excessively large reactions it is really incumbent

upon us (in the present state of our ignorance as to the controlling of the size of a reaction) to endeavor to avoid any reaction. In other words, we belong to the timid rather than to the courageous set. And yet we do not think, with Sahli, that it is necessary to proceed hesitatingly when there is full light upon the path before us. To follow Sahli's scheme strictly, although he himself recognizes that some patients will take tuberculin only with extreme slowness, no patient will go faster than the rigid framework of the scheme allows. On the other hand, in Petruschky's scheme those of Sahli's patients who are abnormally sensitive to tuberculin would be hurried along at too fast a rate. Or, in brief, the rigid scheme of a timid sect will be quite safe for all patients, but will be too slow for those who are less sensitive, and will be for these a loss of time and perhaps of opportunity. *Per contra*, the equally rigid scheme of the opposite tendency will be quite rapid enough for the tolerant ones, but may be ruinously exhaustive for those rather intolerant of tuberculin. We believe, therefore, that it would be better for the progress of tuberculin therapy if the clinicians, instead of grouping themselves into adherents of this or that scheme, would group instead, not themselves, but the patients into the rapid or tolerant and the slow or intolerant. Let each man who gives tuberculin consider himself an agnostic as regards the scheme of dosage to be followed in any given case. Let him feel that he does not know what the patient will or will not tolerate until he actually tries him. This brings us at once to a sound rule of dosage which, instead of being the bugaboo and the terror that current articles and discussions (such as those of Pottenger) make of it, is really a simple and clear proposition, if only the heart of the therapist is set upon the safety of the patient and not upon the dose. Remember what you wish to avoid, rather than the high dose you wish to reach. To para-

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phrase the advice of the author of the nonsense-verses to the hunter after lions—"Keep open eyes for subtle signs"—and these signs are the signs of a tuberculin reaction. They may come from any of three directions—from the focus of infection, from the locus, or site, of injection, and from the general constitution. Watching for a reaction is so important that we must pause here to amplify what the reader already knows, that is, the signs of a reaction. These are: Local—Pain, tenderness, discoloration or swelling at the site of injection; Focal—In pulmonary tuberculosis, increased cough, expectoration, dyspnea, thoracic pain, hemoptysis and extension of the physical signs; Constitutional—Fever, rapid pulse, loss of weight, malaise, headache, chilliness, general hyperesthesia, arthritic pains, gastric or intestinal disturbances, loss of appetite, nausea and vomiting, insomnia, skin eruptions. Of these general signs the most important are pyrexia, loss of weight and symptoms of general depression—most important, that is, from the point of view that very slight changes in the temperature or general body-sense often signal to us that if we raise the dose we shall produce a stronger reaction. These three signals are strongly contrasted by the fact that two are susceptible of easy and rather minute objective measurement, while for evidence of the other we must rely upon a purely subjective phenomenon, the consciousness of the patient. And yet it is well if we pay heed to this subtle sign, as much as to the others, for it is not at all rare that the dose which elicits a strong reaction has been preceded by one which, beyond having caused a vague feeling of not being well, offered nothing tangible as a warning. We must not forget that all avenues must be watched for any of the manifold signs of a slight reaction, which signs are at the same time warnings of a stronger reaction to follow, if they are neglected. (Figs. XII, XIII, XIV, XV, XVI, XVII and XVIII illus-

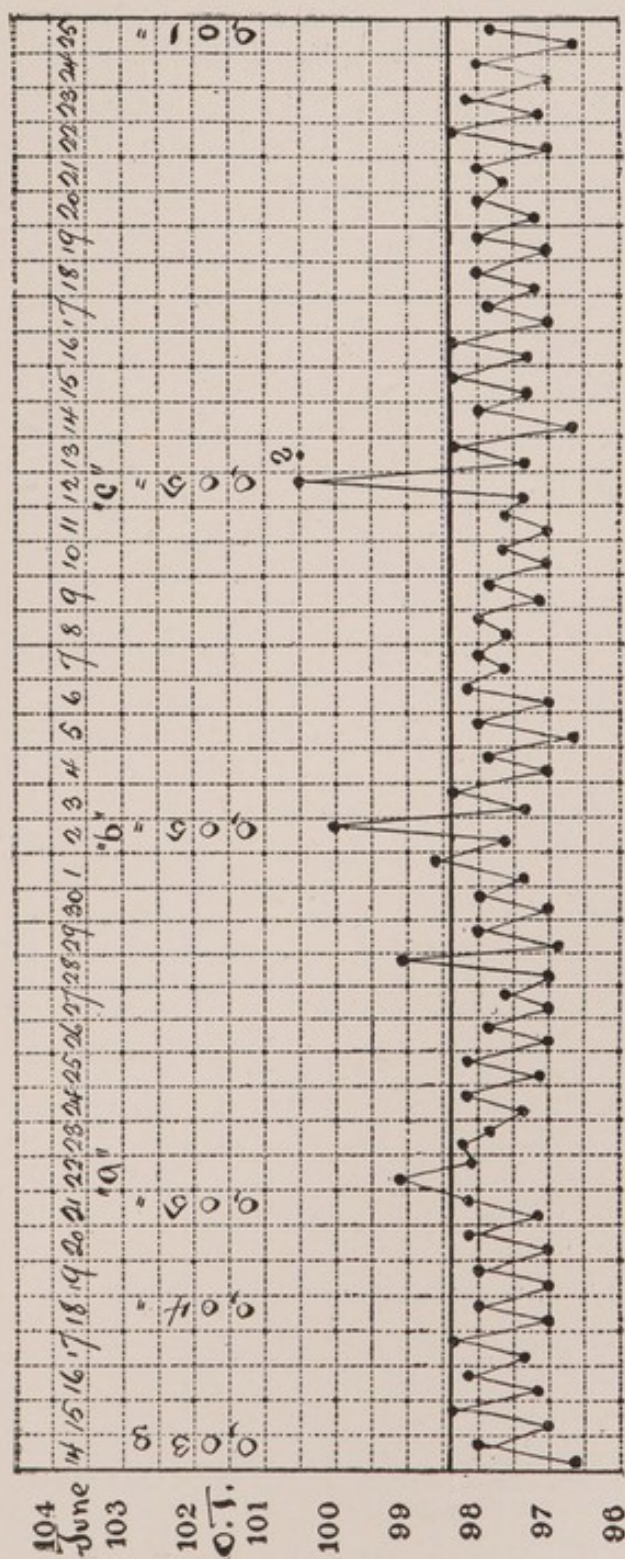


FIG. XII.—CASE No. 1077. At *a* there is a typical reaction to 0.05 gm. followed by a still more severe reaction to the same dose at *b* and *c*. At *c* the patient felt too ill to take his temperature but is confident that it was much higher than during the two preceding reactions. During these reactions there was no increase in the physical signs and patient's general condition did not suffer.

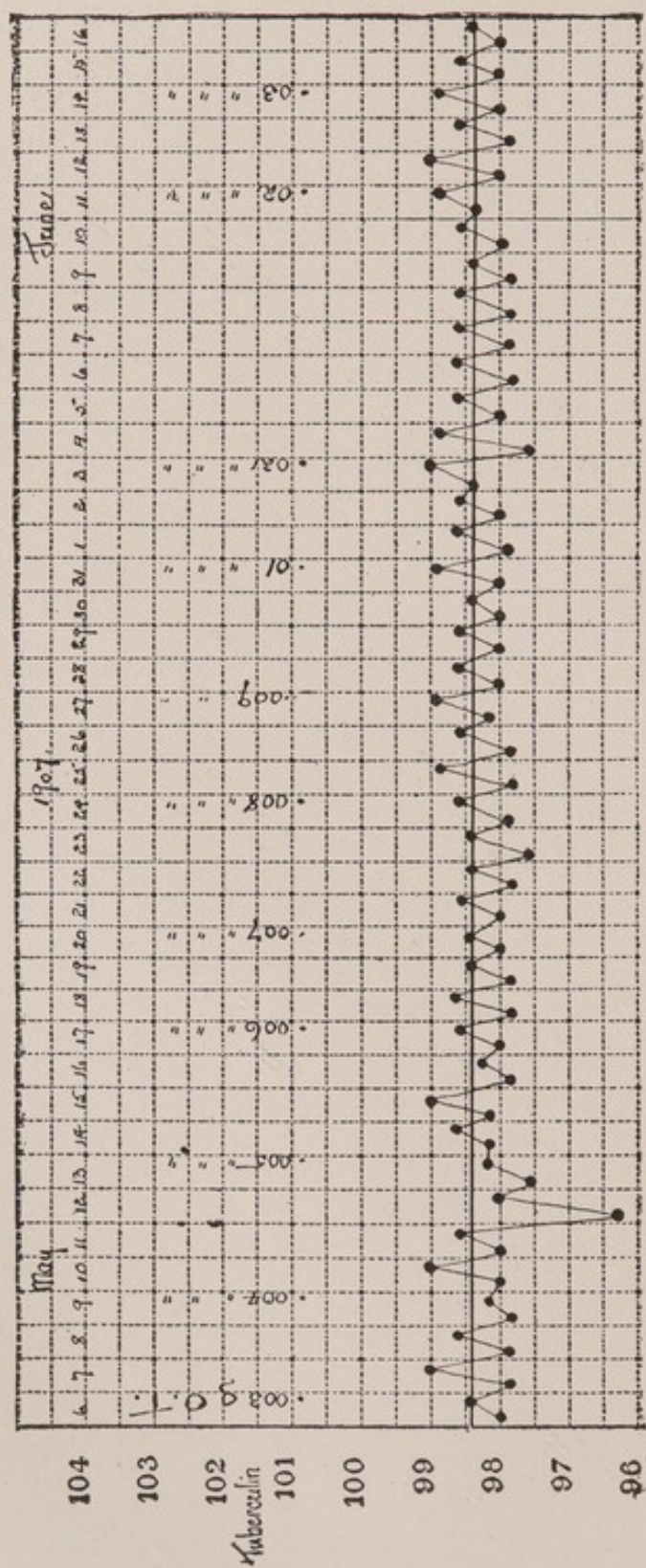


Fig. XIII (a). —Case No. 1290.

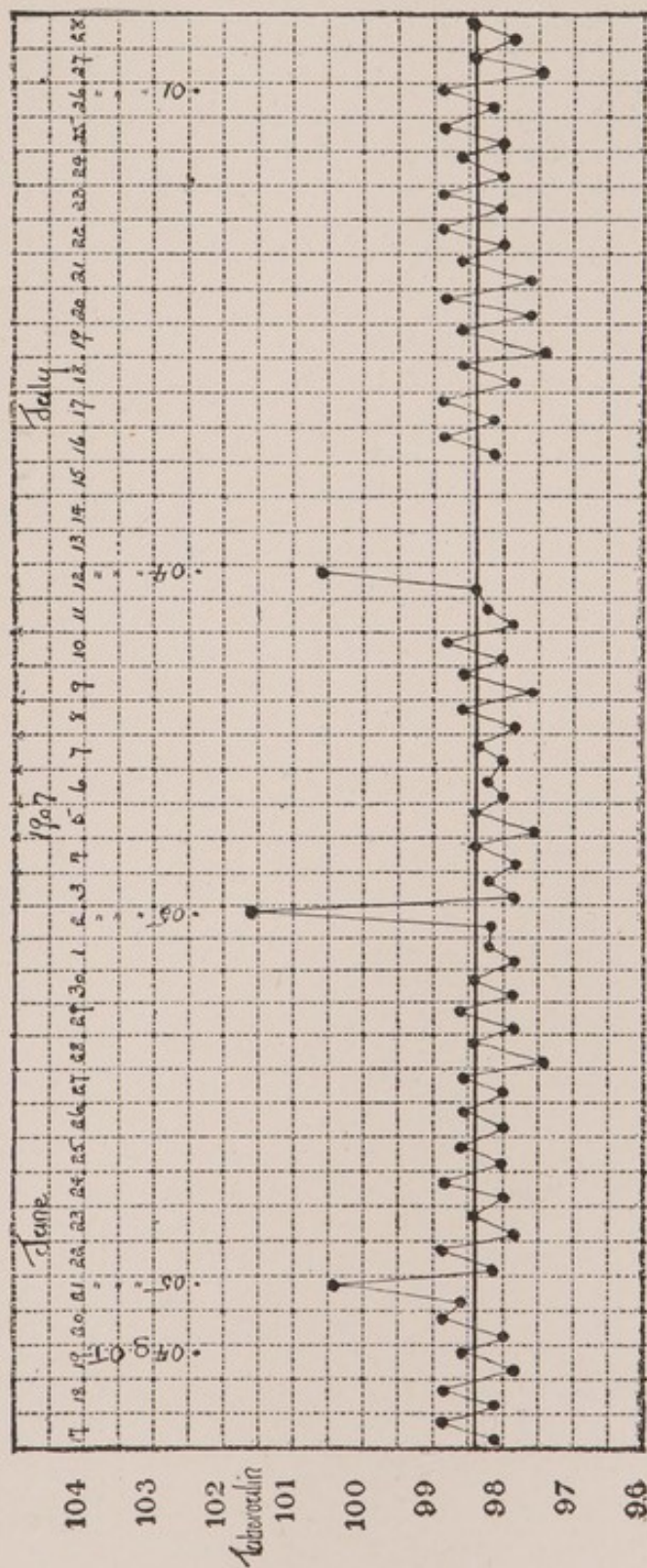


FIG. XIII (b)—Case No. 1290.

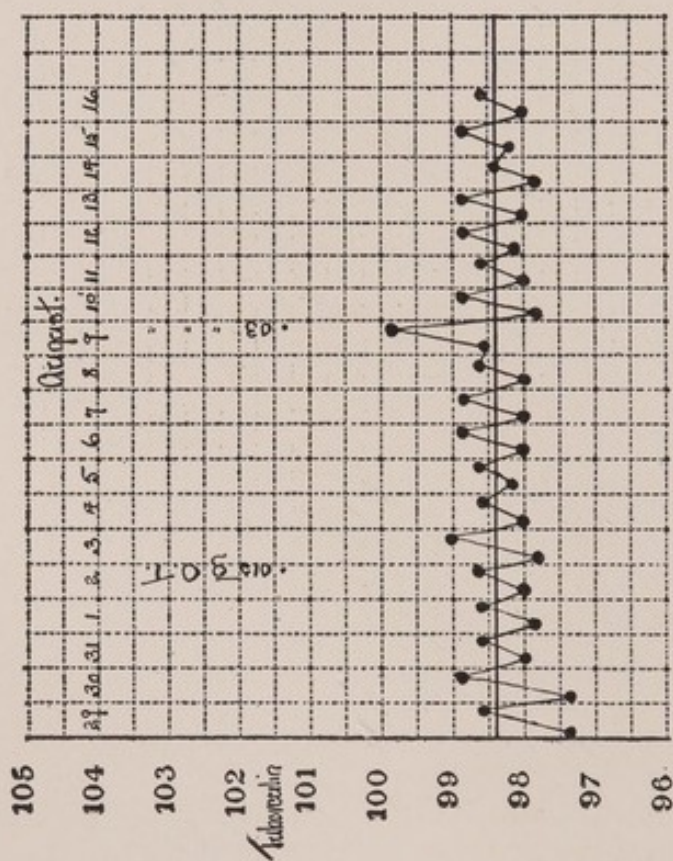


FIG. XIII (c).—CASE No. 1290. On May 7 and 9 there is a slight febrile reaction with local pain and swelling. On the 15th following 0.005 gm. there is another slight reaction. On the 21st cough is increased after 0.007 gm. On the 25th and the 27th and the 31st and the 3d of June there are slight febrile reactions and on June 3d he had headache and general malaise. There is another slight reaction on the 12th after 0.02 gm., although there were no constitutional symptoms. After 0.05 gm. there is a marked reaction followed by a still more severe reaction upon the repetition of this dose. There is a third reaction to 0.04 gm. and on August 9 a reaction to 0.03 gm.

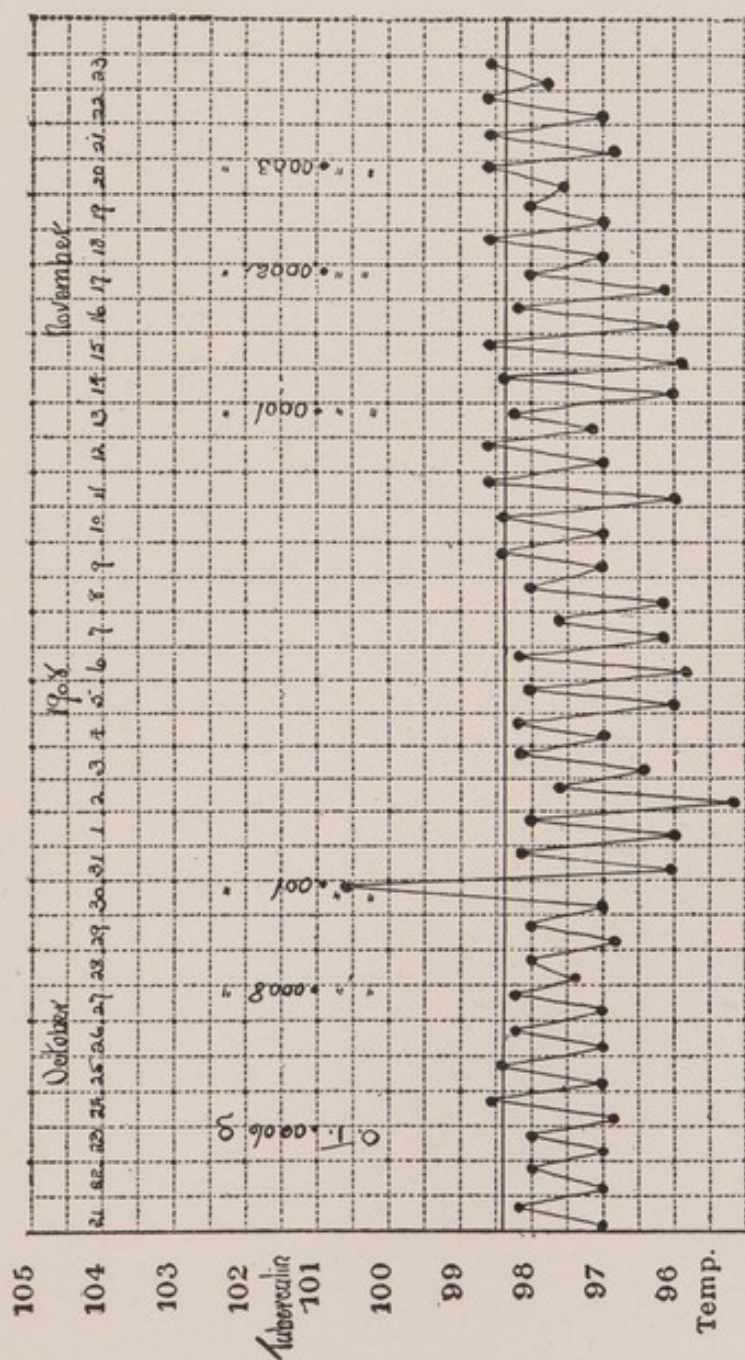


FIG. XIV.—CASE No. 2162. On October 30 when 1 mg. was given it was noted that a large area of infiltration was still present from the previous injection although the patient made no complaint of it. The 1 mg. should not have been given. After decreasing the dose and then ascending the 1 mg. mark was gradually passed.

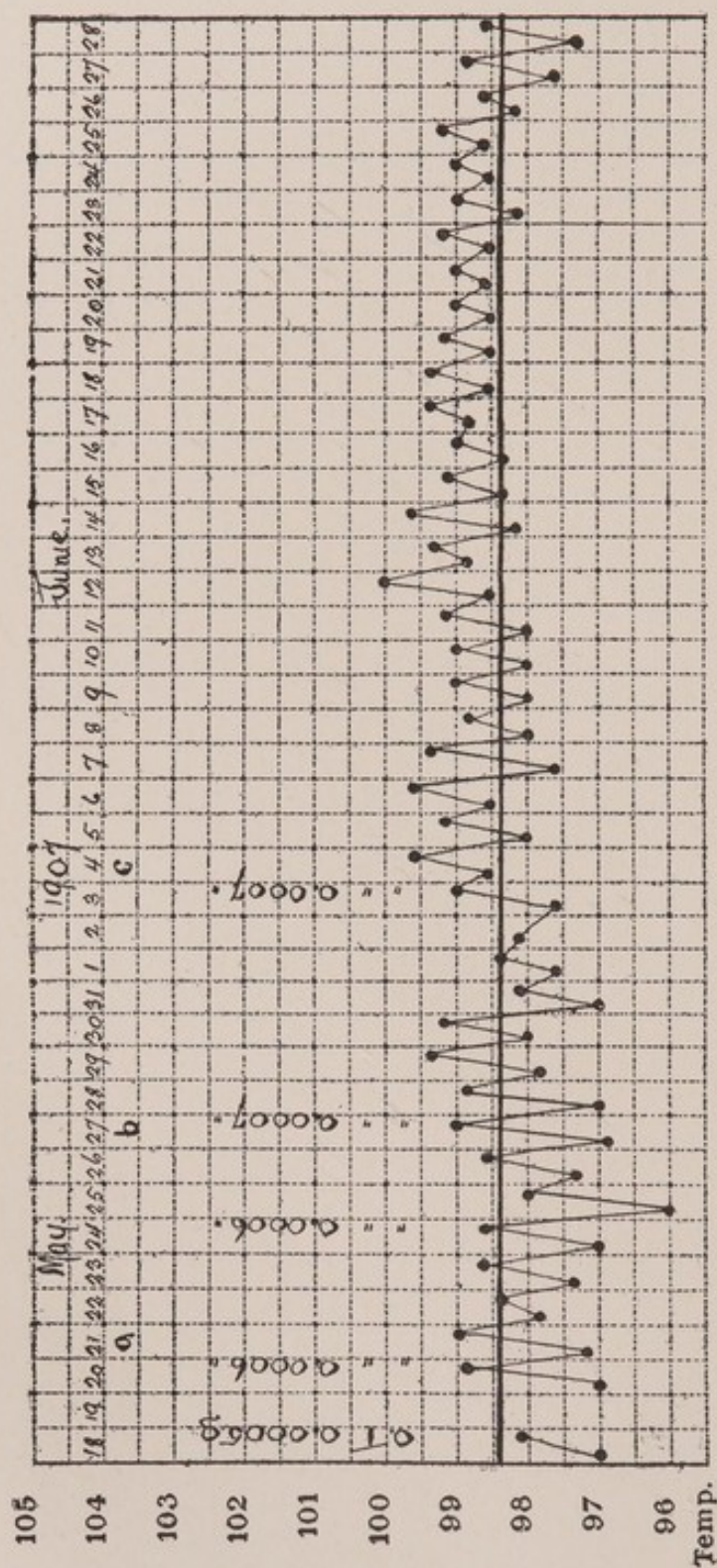


FIG. XV.—CASE No. 1388. At *a* there is a slight rise of temperature after 0.0006 gm. When this dose is repeated there is no reaction. At *b* there is a definite elevation of temperature for three days following the injection and on May 31 no injection was given. At *c* after a repetition of the same dose a not severe but a prolonged reaction is induced, associated for the first few days with constitutional symptoms.

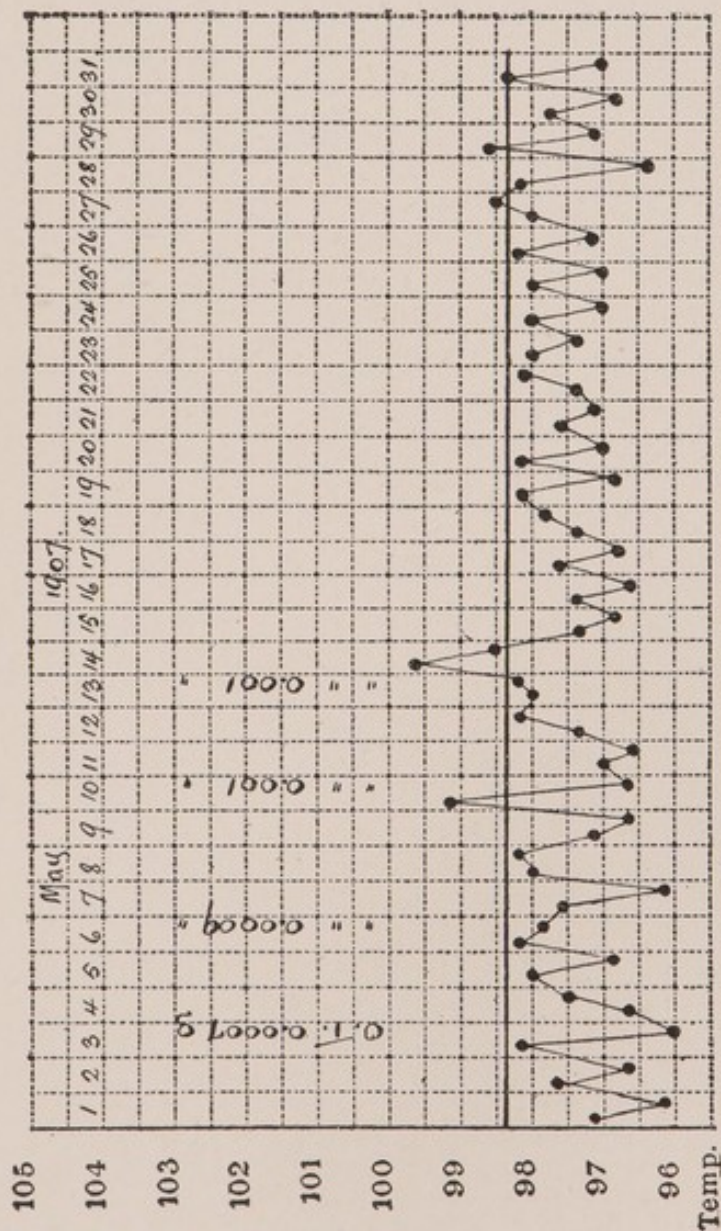


FIG. XVI.—CASE No. 1151. On May 10 there is a mild reaction to 0.001 gm. and a more severe reaction on the 17th when the dose is repeated.

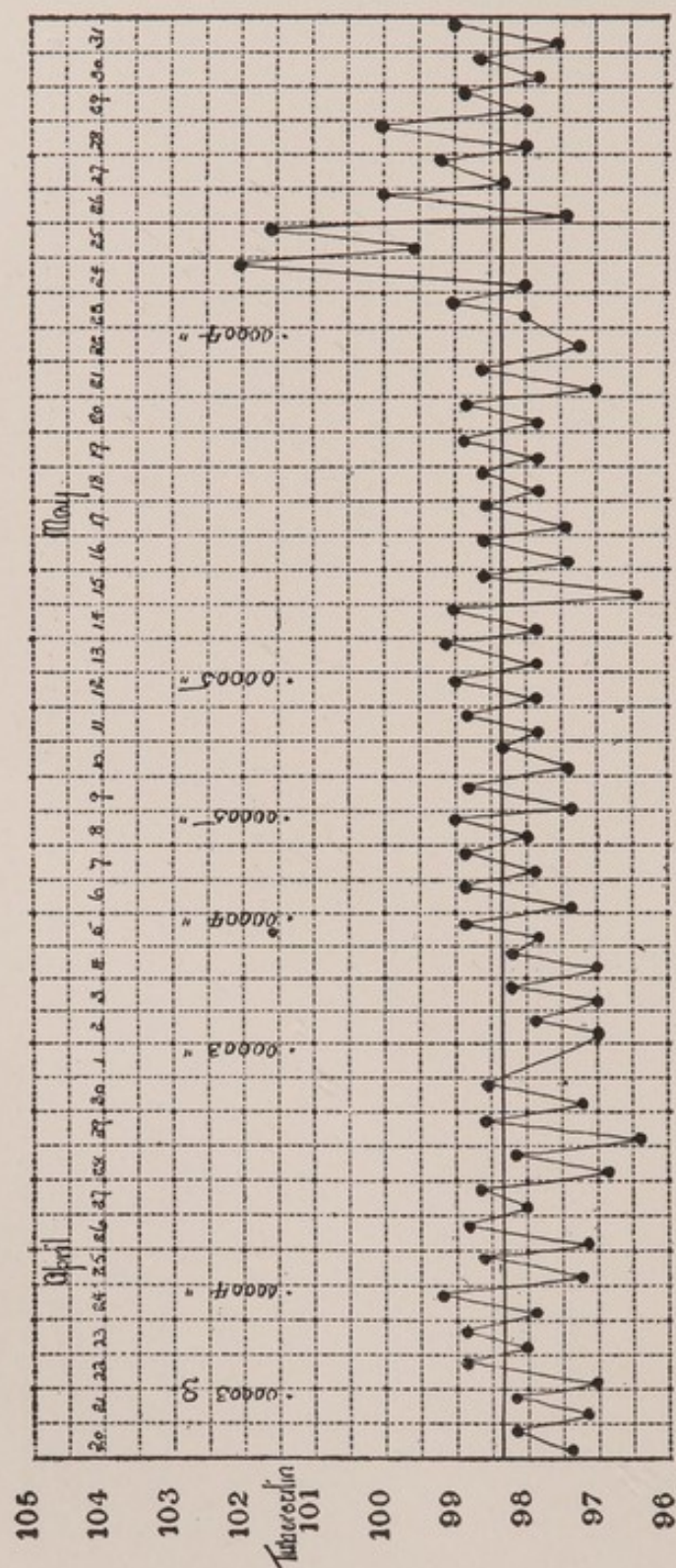


FIG. XVII.—CASE No. 2162. A reaction to 0.000,04 gm. after several previous slight reactions.

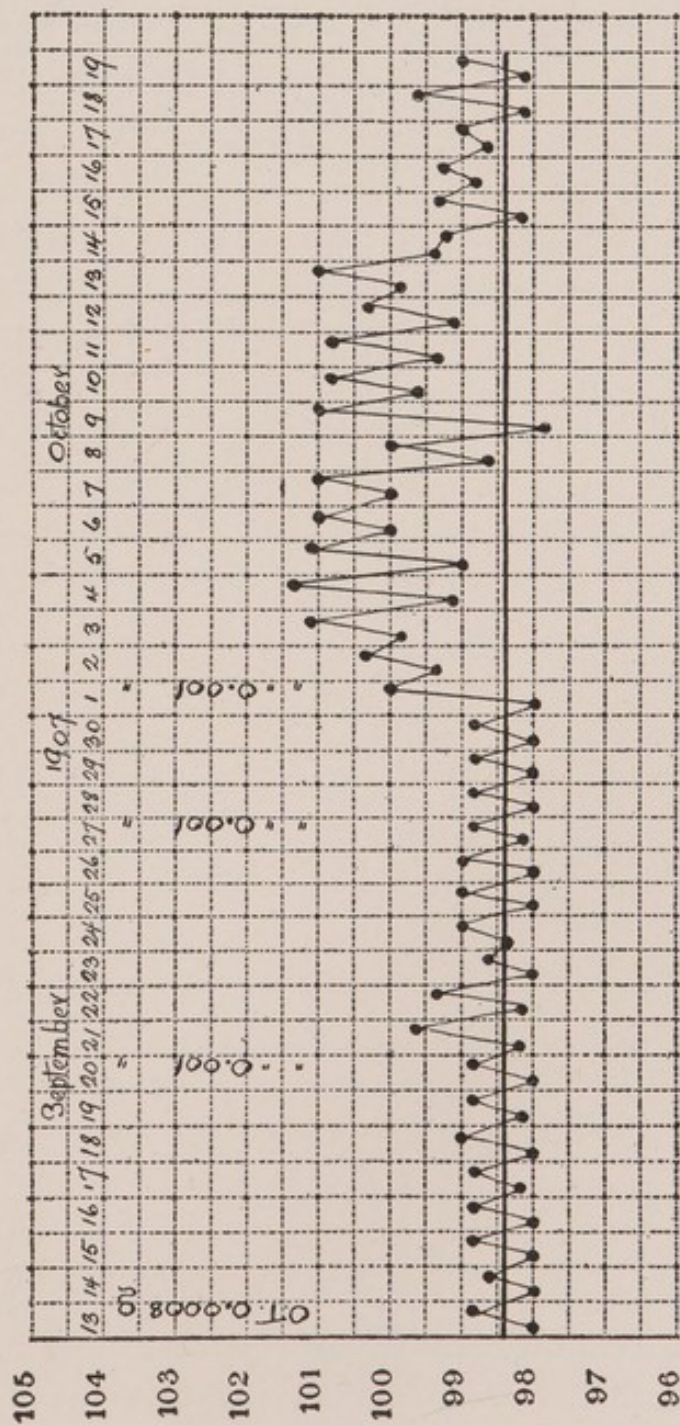


FIG. XVIII.—CASE No. 1542. A prolonged reaction after the third dose of 0.001 gm. There had previously been a slight reaction after the same dose.

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trate reaction after such neglect.) As for the temperature, the smallest fraction of a degree recorded by the clinical thermometer is to be noted, and any such rise above what has been the usual maximum temperature of the previous days should be looked at askance. It is also well to note whether for any particular time of the day the temperature is above what it has usually been, although this alone need not cause any slowing of the treatment. It is the maximum daily temperature which is important, especially if the heretofore maximum temperature has been very close to the upper normal limit. On the other hand, if the customary daily maximum has been rather far below the upper normal limit, a rise of the maximum line need not, in itself, cause alarm, as long as it remains subfebrile. When we say that a rise above the usual maximum temperature should not be neglected, we do not mean that in itself a small rise contraindicates an increase of the dose. But we do mean that now it is especially imperative to watch closely for additional signs of a reaction. If additional signs do appear it is advisable to retard the dosage, since a coincidence of signs, though each be small, is especially a warning of the proximity of a reaction, unless we relax our pushing of the tuberculin. Since pyrexia is the only one of the constitutional signs susceptible of minute measurement, it alone of these signs permits of some dalliance. Should any of the other signs of a constitutional disturbance appear, it is imperative to apply the brakes. For in our experience it is much less customary for even a slight constitutional sign not to indicate an approaching reaction than for a slight rise of the temperature above normal not to do so. The latter occurrence, if solitary, is not so threatening. It is at times a question of the greatest difficulty to decide if tuberculin is responsible for a particular temperature elevation. We know how common it is for patients with pulmonary tuberculosis to have temporary

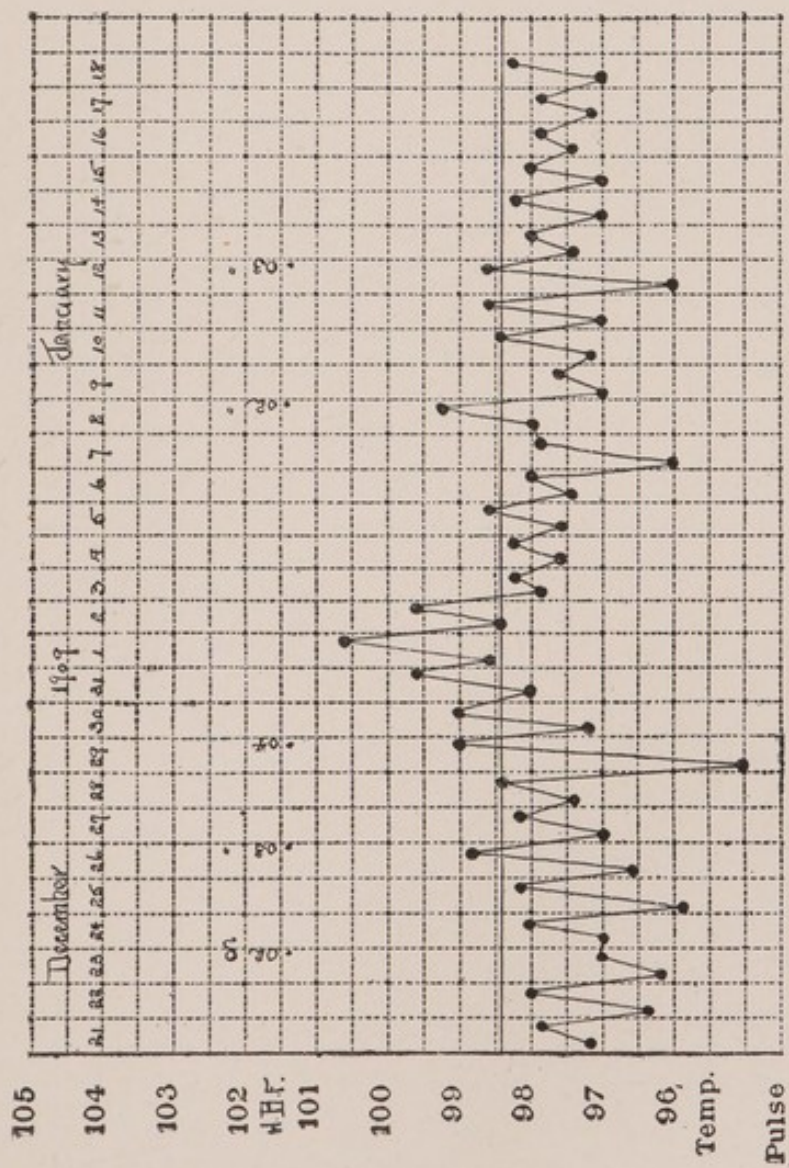


FIG. XIX.—Case No. 2089. The reaction of January 1 was associated with tonsillitis and was not due to tuberculin injection.

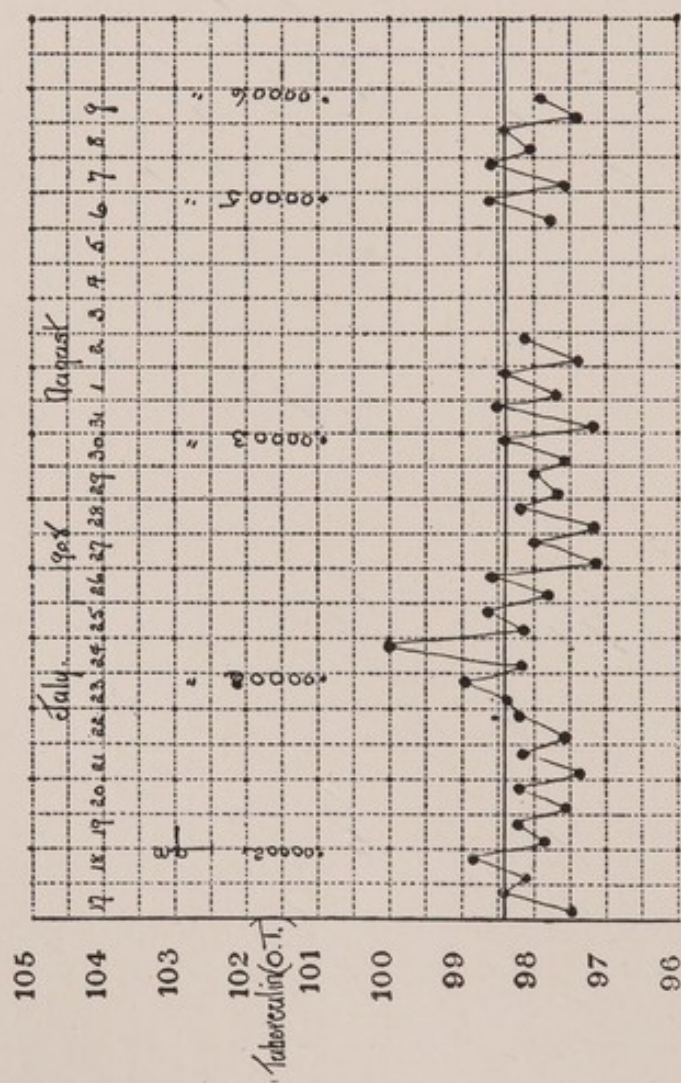


FIG. XX.—CASE No. 1532. On July 24 there is a rise of temperature which has the appearance of a genuine tuberculin reaction. The patient, too, had general constitutional symptoms. However, on the same day he developed an attack of tonsillitis. The fact that there is no reaction when the same dose is repeated is a point against its being a tuberculin reaction.

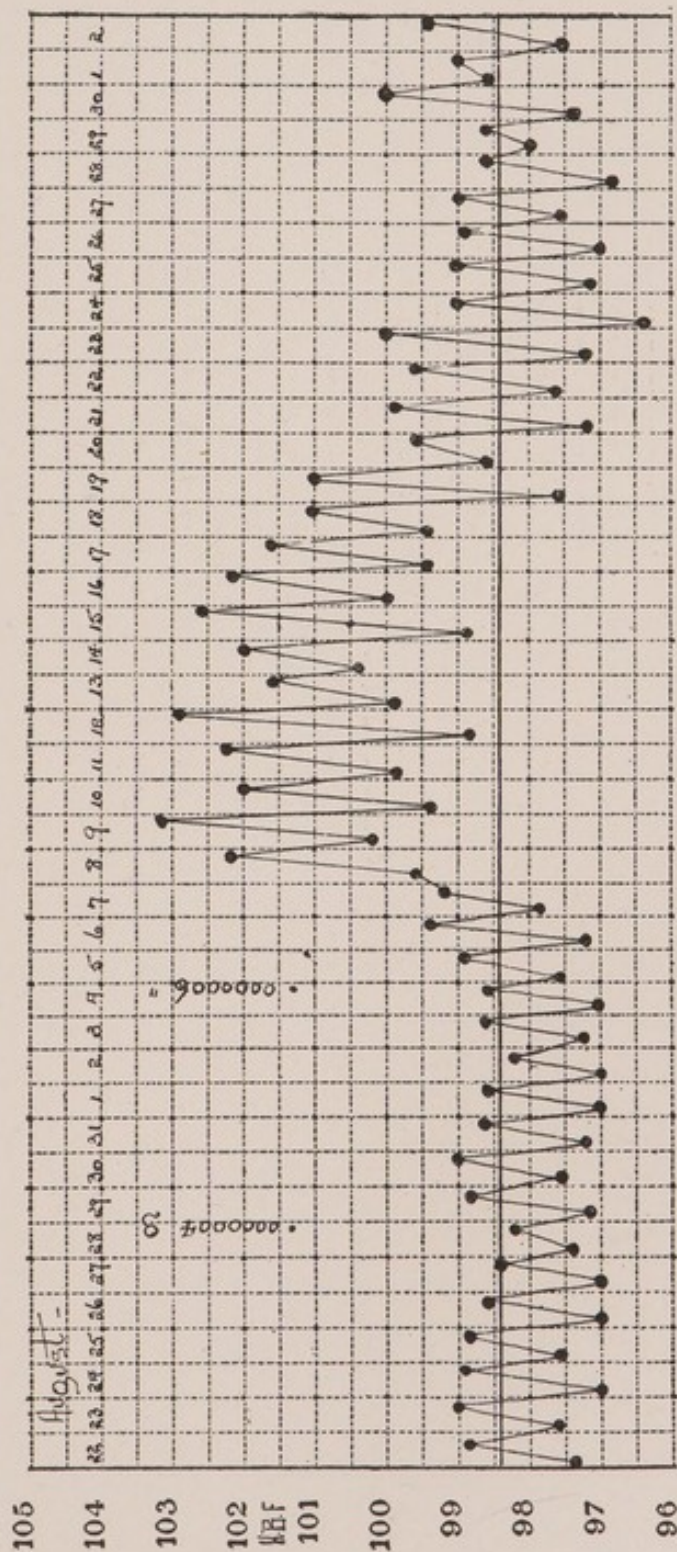


FIG. XXI.—CASE No. 3011. This febrile reaction is certainly quite independent of tuberculin. The temperature did not rise until four days after the injection and there were no local manifestations. The patient had symptoms of grip.

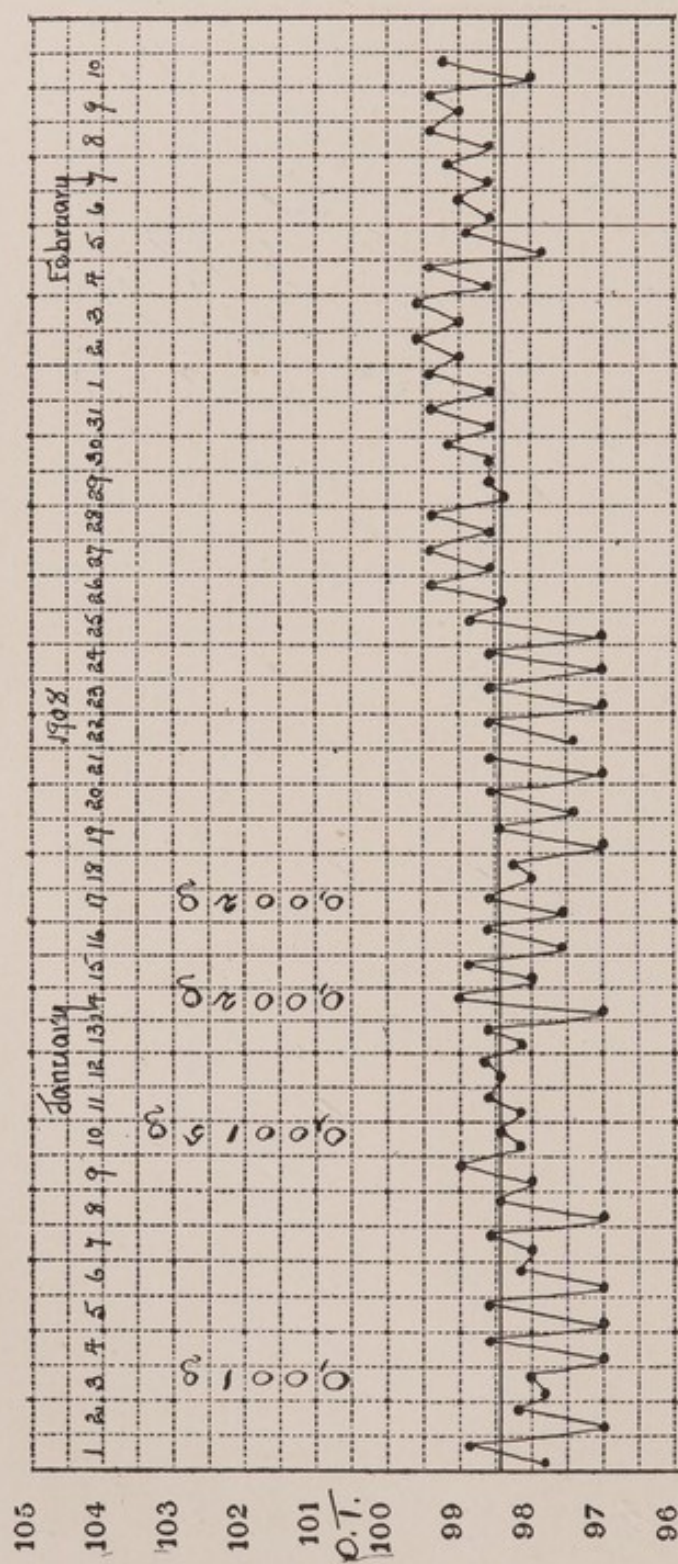


FIG. XXII.—CASE No. 394. Patient began to feel ill on January 21. Headache and pains over the body, and pain in bones. The rise of temperature marks the onset of secondary symptoms of lues.

flare-ups of fever when they are not being treated with tuberculin. Such elevations may have all the characters of a tuberculin reaction artificially produced, and indeed are essentially the same thing. Intercurrent infections too must be considered. The latter group are, as a rule, easily distinguished. Figs. XIX and XX show the fever from tonsillitis; Fig. XXI from grip; Fig. XXII from syphilis. No definite decision can be made in some instances belonging to the first group. Denys refuses to consider any temperature elevation as due to tuberculin which comes on more than 48 hours after the injection. It is characteristic of tuberculin reactions that the rise is abrupt even though the fall may be irregular and prolonged. A fever coming on with step-like progression, so that the fastigium is not reached until the third or fourth day, is unlikely to be due to the tuberculin injection. We have become so impressed with the almost constant appearance of a local reaction to injections preceding the ones liberating a general reaction that we would hesitate to ascribe an elevation coming suddenly in the midst of a perfectly smooth tuberculin treatment and unaccompanied by a local reaction to the injections, provided, of course, that the dose has not been unduly increased. Figs. XXIII and XXIV show such questionable febrile reactions.

It is of course obvious that the point of view from which a reaction is regarded is not the same for the user of tuberculin diagnostically and therapeutically. The diagnostician aims at definite reactions, since an indefinite reaction may properly have its nature questioned. Inversely, the therapist fears even indefinite reactions. The former must suspect that things are not what they seem; the latter must fear things are worse than they are. Therefore the signs of a reaction for the therapist are more subtle phenomena than for the diagnostician, and, therefore, too, although a tuberculin reaction remains a tuber-

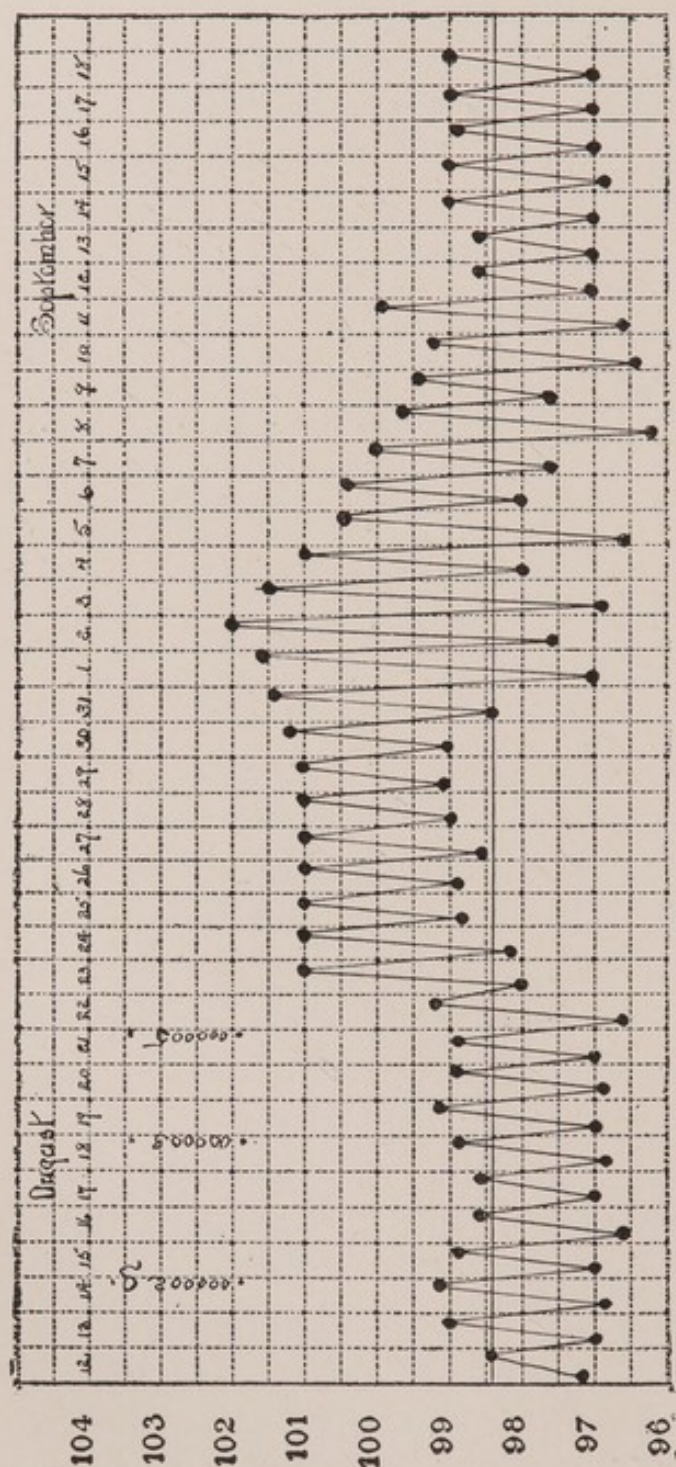


Fig. XXIII.—CASE No. 2316. It is difficult to say if this febrile elevation has any relation to tuberculin. The patient did not have pain or swelling at the site of injection and had previously shown no signs of developing intolerance.

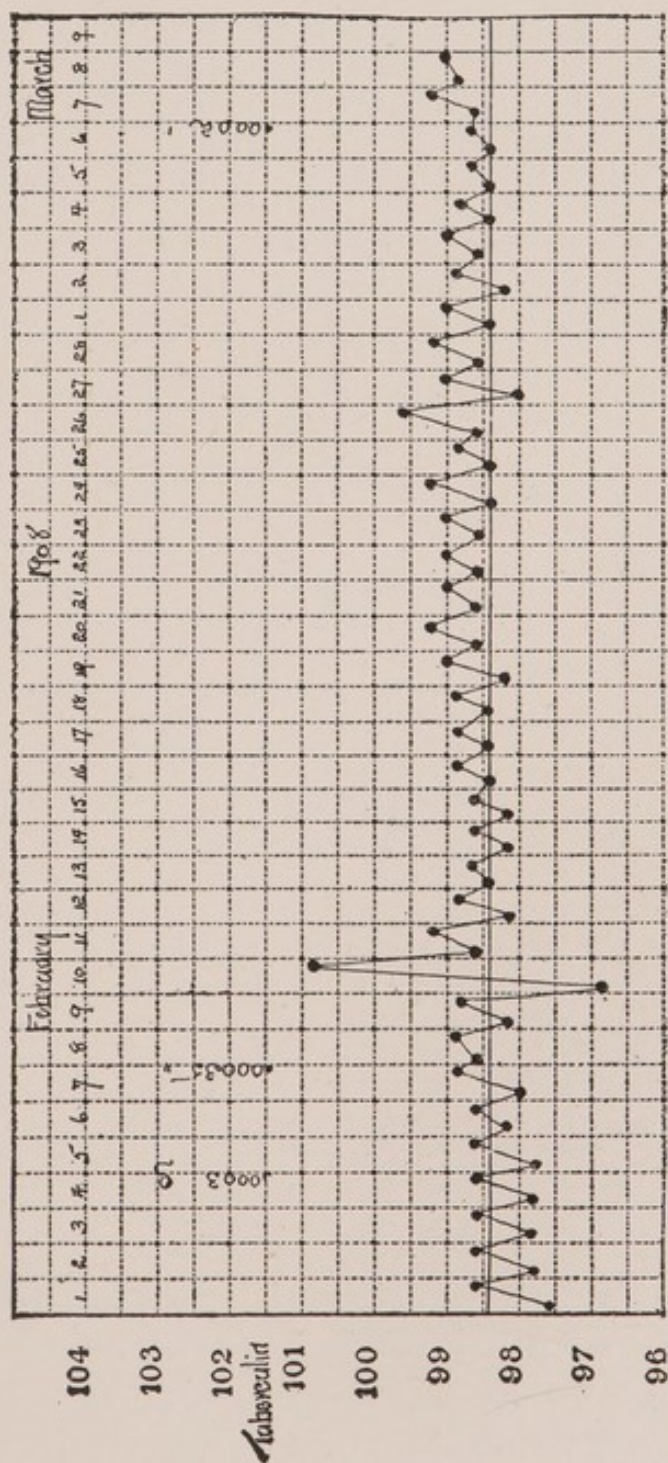


FIG. XXIV.—CASE No. 1967. This chart is interesting because there is no special rise of fever until seventy-two hours after the injection. It might be questioned whether this was a genuine reaction. It was not preceded by premonitory symptoms. However, after the injection of March 6 there was a slight rise of temperature with marked pain and swelling at site of injection, showing that the sensitiveness to tuberculin had been greatly increased.

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culin reaction, we are here discussing the less rather than the more obvious signs of a reaction, and really a slight, indefinite, rather than a sharp, clearcut reaction. And this because of the necessity for caution, and because of the fact that we are treating definite cases with lesions that are immense, as compared with the dubious signs that engage the attention of the man who seeks a diagnostic reaction.

Loss of weight is a delicate sign, and may appear long before any other sign of intolerance. It is, however, more valuable as a sign of overdosage, late in treatment, than as a protection against the usual suddenly appearing reactions.

The following illustrates a loss of weight apparently due to overdosage:

F. L., age 22, No. 5,395.

1910.

Nov. 1. B. F. 0.300 c. c. Wgt. = 119 lbs. T. to 99°. No local pain or swelling. Depression.

" 8. " 0.300 " T. to 99. No local or general reaction.

" 22. " 0.400 " Wgt. = 119 lbs. T. to 99. Slight local tenderness.

Dec. 6. " 0.500 " Wgt. = 117 lbs. T. to 99. No local reaction.

" 20. " 0.600 " Wgt. = 116½ lbs. T. to 99. No local trouble.

" 27. " 0.700 " Wgt. = 115 lbs. No trouble.

1911.

Jan. 10. " 0.700 " Wgt. = 115 lbs. T. to 99°.

Tuberculin was now discontinued, on account of loss of weight, and slight rise of temperature.

Bandelier and Roepke regard an increase in the pulse-rate as a solitary signal of great importance. We have not ourselves been able to observe this sign as at all frequent, nor has Lawrason Brown.

Local signs manifest themselves as changes at or near the mark on the skin that shows where the needle of the tuberculin syringe penetrated the integument. They con-

sist of all the gradations between an invisible thickening of the skin, apparent only after careful examination, by rolling or pinching the cutaneous area in question between two finger-tips, and a wide, deep, hard node which to the patient is painful and tender, and to the beholder angry looking and inflamed. Such a node becomes, after days, less tender and painful, the thickening slowly thins, and the angry red fades gradually to a sullen blue and finally to a yellow. The lymph-nodes that drain the cutaneous area involved in such a local reaction may be tender and swollen, but the relation is not constant in either direction, the glands sometimes being swollen when the local reaction is slight, and the swelling entirely absent when the latter is large. As a rule, the glands are not involved—at least to an extent that is recognized by the patient himself.

The local reaction has assumed great importance in recent years, especially since the emphasis laid upon it by Denys. This author called attention to the extreme value of the local reaction as a warning of the approach of a general reaction. The value of this sign is enhanced by the fact that it is more often solitary than any other sign; that is, it more often occurs alone, without any other sign or symptom. However, if a dose which elicits a local reaction is followed by a larger dose, or if the same dose repeated gives even a greater local reaction, a general reaction is apt to occur. (See Fig. XIV.) In other words, if upon the appearance of a local reaction the dose is diminished or halted, then a general reaction is an extremely rare phenomenon. But if the solitary local reaction is unheeded, and the administrator waits for some constitutional symptom before slowing, he may meet with a general reaction of more or less virulence, without having had any preliminary constitutional symptoms. For a large general reaction may have as its prodrome only a moderate local reaction unaccompanied by fever or general distress of any

kind. And, although it is well to regard all reactive signs in deciding upon the next dose, yet the local sign is so delicate that in the case of patients so situated as not to furnish a temperature record it is safe to proceed with the sole guidance of the local reaction, subjective and objective. In some patients a local reaction is simulated after the injection of large doses of undiluted O. T. or B. F., i. e., when the dose is in the neighborhood of 500-600 mg. This simulation is due merely to the bulk and concentration of the dose, and is not a real local reaction. It can be avoided by dividing the dose into two injections given at the same time, but not into neighboring areas of skin.

How to Avoid Reactions.—Saathoff¹ claims a parallelism between the local reaction and a focal reaction, and this claim is stoutly fought by Bandelier and Roepke on the basis of their observations in pulmonary tuberculosis, and especially in lupus. However, the value of this sign as a guide for the increase or decrease of the dose is not affected by the status of the argument as to a strict parallelism between the local and focal reaction. It is enough to know that clinically, if observed, it enables those who desire it to avoid general reactions.

Our observations are concerned with the local reactions in the back. In the forearm the sign is, in many people, too delicate. Perhaps on account of the tenseness of the skin in the forearm the local reaction there partakes more of the nature of an intracutaneous reaction than when it occurs in the roomy, cellular subcutis of the back.

The focal pulmonary signs of a reaction are of course an indication that we have gone faster than we wished. And our extreme desire to avoid constitutional reactions is based on the fact that they are accompanied by focal reactions of no slight degree, even if not evidenced by focal

¹ Saathoff: *Tuberkulindiagnostik und Therapie nebst Stoffwechselsuchen bei der Tuberkulinreaktion.* München. med. Wehnshr., 1909, lvi, 2041.

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signs or symptoms. It must be remembered, however, that what we desire to avoid are the focal pulmonary reactions that are large enough to manifest themselves by changes in the physical signs or by decided symptoms. We do not wish to avoid the slight focal reactions. Quite on the contrary, it is the production of such slight reactions that, as has already been shown, constitutes the most valuable result of tuberculin therapy. It is therefore incumbent upon any one using tuberculin not to be too cautious. We must strongly urge the avoidance of a manifest reaction, and for that reason have given rather minutely the warning signals. But we at the same time urge that the tuberculin be given rapidly enough to produce from time to time some slight warning signal. Almost invariably this will be a slight local reaction (at the site of injection). When this is once obtained it is well to go more slowly. But if dose after dose produces not even the slightest local reaction, or any sign of hypersensitiveness, it is desirable to increase the doses more rapidly than heretofore; not because we have been doing harm, but lest we miss producing the mild focal reaction, and thus rob the patient of his due.

Dosage.—It may seem strange to the reader that as yet nothing has been said of the size of the dose itself. This neglect has been intentional, with the purpose of fixing the fact that the important thing is not the dose but whether the dose should be increased or lowered. In brief, the object is not to give a certain dose but to give as much as the patient can tolerate without a visible reaction. With this premise for our guidance, the question of the size of the initial dose resolves itself into the question, "What can a patient tolerate whose susceptibility to tuberculin is to us an unknown quantity?" Of course we cannot answer this question, and, since we cannot answer it, we must fix the initial dose so small that none of our patients is likely to be harmed by it. The size of this dose is based on em-

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pirical data. It is no doubt smaller than what many of the patients can tolerate, but then experience has shown that no patients are harmed by it, and those whose tolerance is greater can quickly be distinguished from the more sensitive ones.

As regards the sites of the initial dose, patients can be divided into three classes. A. Children; B. Patients who have a slight pyrexia, or are not in good condition; C. Patients in good condition and without fever. The first two classes receive smaller initial doses than apyretic adults, in good general condition. Only rarely do the lower limits in the appended table cause a reaction, even in children. The smaller initial dose is for classes A and B; the larger for class C.

TABLE OF THE USUAL INITIAL AND MAXIMAL DOSES FOR THE
COMMONLY USED TUBERCULINS ¹

| TUBERCULIN | INITIAL DOSE | | | | MAXIMAL DOSE |
|------------|---------------------|----------|-------------|-------|----------------|
| O. T. | 0.000,000,1 | c. c. to | 0.000,001 | c. c. | 1.0 c. c. |
| T. R. | 0.000,001 | " " | 0.000,1 | " " | 2.0 " |
| B. E. | 0.000,001 | " " | 0.000,1 | " " | 2.0 " |
| B. F. | 0.000,000,01 | " " | 0.000,000,1 | " " | 1.0 " |
| Béraneck's | Of A/32, 0.05 c. c. | | | | Of H 1.0 c. c. |

Béraneck's tuberculin is marketed, already diluted, in a series A/128, A/64, ... A/4, A/2, A, B.....H. H is the

¹ There has been some confusion in the literature as to the use of solid and liquid measures in indicating amounts of tuberculin. There is now a tendency to express all amounts in terms of cubic centimeters and not in grams. This is done because, in making dilutions, the tuberculin is not weighed but measured. Moreover, the amount of solid substance per volume of tuberculin varies with the different tuberculins, as has been stated. In fact, when the terms 1 mg. of O. T., or 1 mg. of T. R., etc., have been used by writers, it was commonly implied that 1 c. c. of the original solution contained always 1 g. This is not nearly true, but has been only a convenient assumption. It will, therefore, be better to employ the liquid measure entirely, using c. mm. for mg. On account of the common use in this country of the symbol mg., we have in places yielded to the current tendency as a compromise, for the sake of clearness.

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pure tuberculin. Each solution is one-half the strength of the next stronger. The increase of dose is usually by 0.1 c.c. until 0.5 c.c. is given. Then 0.1 c.c. of the next stronger solution is given, and so on.

In diluting T. R. normal salt solution without phenol is used. The suspension of T. R. and B. E. should be violently shaken before each dose is extracted, whether for injection or for making further dilutions.

Brown gives the smallest initial dose that caused a reaction as $1/10,000$ mg. of B. F., but during the period of hypersensitiveness that comes at times during treatment $3/100,000$ mg. B. F. We ourselves have seen a local reaction after $1/1,000,000$ mg. and in children a local and slight general reaction after $1/2,000,000$ mg. If a patient is given treatment immediately after a constitutional tuberculin reaction extra caution is needed as to initial dosage, since such patients may be in a condition of hypersensitiveness. White and Van Norman make the initial dose equal to the quantity of tuberculin which, when applied cutaneously, will elicit a minimal reaction after 72 hours. Such a dose given intracutaneously, they say, will elicit a local but no constitutional reaction. They find that some patients tolerate an initial dose 100 times as large as others. They do not increase the subsequent doses, but repeat the initial dose every fourteen days. There are many arbitrary assumptions, however, in their scheme and reasoning.

Interval Between Doses.—The interval between injections is 3 to 4 days. Two injections are usually given per week. This interval, too, is an empirical one, although some laboratory basis exists in the data of the opsonic index. Wright's work has shown that the negative phase following the introduction of a vaccine, with the development of the ensuing crest, consumes about 3 to 4 days. Without committing ourselves as to the value of the opsonic

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index, there are many clinical subjective data as to the feeling of depression on the day following inoculation and the wave of elation on the third or fourth day. But the most practical reason for the 3-to-4-day interval is that such a lapse of time is ample to allow the occurrence of a reaction if there is to be one. While most reactions set in within 24 to 36 hours, some may begin as late as 48 to 60 hours after the dose is given. (L. Brown.) By waiting at least 3 days we are assured that, if by that time no reaction has occurred, none will occur. To shorten the interval is dangerous, although this has been done and is still advised by some.

The usual interval is maintained as long as the patient is doing well. At a certain stage it is not uncommonly found that the patient begins to be intolerant. He gets slight reactions, or there may be simply depression or a loss of weight. In such patients the lengthening of the interval to one week often permits continued increase of the dose with continued improvement of the patient. Indeed, so frequent has this occurrence been that it is not an unwise procedure spontaneously to increase the dose interval to one week, when the dose of 50 mg. B. F. is reached. For O. T. the change occurs at about 100 mg.; for B. E. and T. R. at about 200 mg. In this wise is avoided the exhaustion which may follow the continued stimulation of the body to the formation of reactive substances. With very sensitive patients it is well to make the interval a week or ten days from the very beginning of treatment, or even greater.

In addition to the signs of overdosage, which are not uncommon when 50-100 mg. are reached, Brown finds a period of increased susceptibility or hypersensitiveness for B. F. at 1/100 to 1/10 mg.; and for B. E. or O. T., at 1/10 mg. Here, too, caution is necessary. We ourselves have not noticed such a period, nor have Bandelier and Roepke.

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We have not found it necessary to increase the interval for children. After a wise initial dose has been selected, the child is able to take tuberculin as rapidly as the adult.

In case of a reaction no tuberculin should be given until the reaction has completely disappeared, and, if slight reactions continue to appear, even with diminished dosage, the interval should be lengthened to one or two weeks. If trouble still occurs, the patient must be adjudged hypersensitive, and treatment interrupted for some months.

The following case illustrates the value of an interruption in the treatment in order to overcome a hypersensitiveness. See also Figure XXV.

1908.

| | | | | | |
|------|-----|-------|-----------------|-------------------------|-----------------------------|
| May | 1. | O. T. | 0.000,008 c. c. | T. below 99. | No reaction of any kind. |
| " | 5. | " | 0.000,009 " | T. to 99. | Slight local pain. |
| " | 12. | " | 0.000,01 " | T. to 99 ^s . | Local and general reaction. |
| " | 29. | " | 0.000,009 " | T. to 99 ^s . | Slight general reaction. |
| June | 5. | " | 0.000,001 " | T. below 99. | All well. |
| " | 9. | " | 0.000,002 " | T. below 99. | All well. |

Beginning with the initial doses above stated and proceeding at the stated interval, if there appear none of the signs of a reaction, if the patient is not losing weight and gives no sign whatever of untoward effect from the tuberculin, the dose is increased each time. The amount of increase is a matter of judgment, and this judgment is based always on a close observation of the patient and a knowledge of the empirical data. Using the decimal system of dilutions, as described in Section II, a safe arbitrary scheme is to increase by 0.1 c. c. Thus, if 1/1,000 mg. of O. T. = 0.1 c. c. of Solution VI, then 2/1,000 mg. (0.2 c. c.) will be the next dose. Then 0.3, 0.4, 0.5, . . . 0.9 c. c. The next dose, 1.0 c. c. will be the same as 0.1 c. c. of the next stronger solution, No. V, which latter is, of course, used instead of 1 c. c. of VI, which is unnecessarily bulky. The reader will observe that if 0.1 c. c. of Solution V is fol-

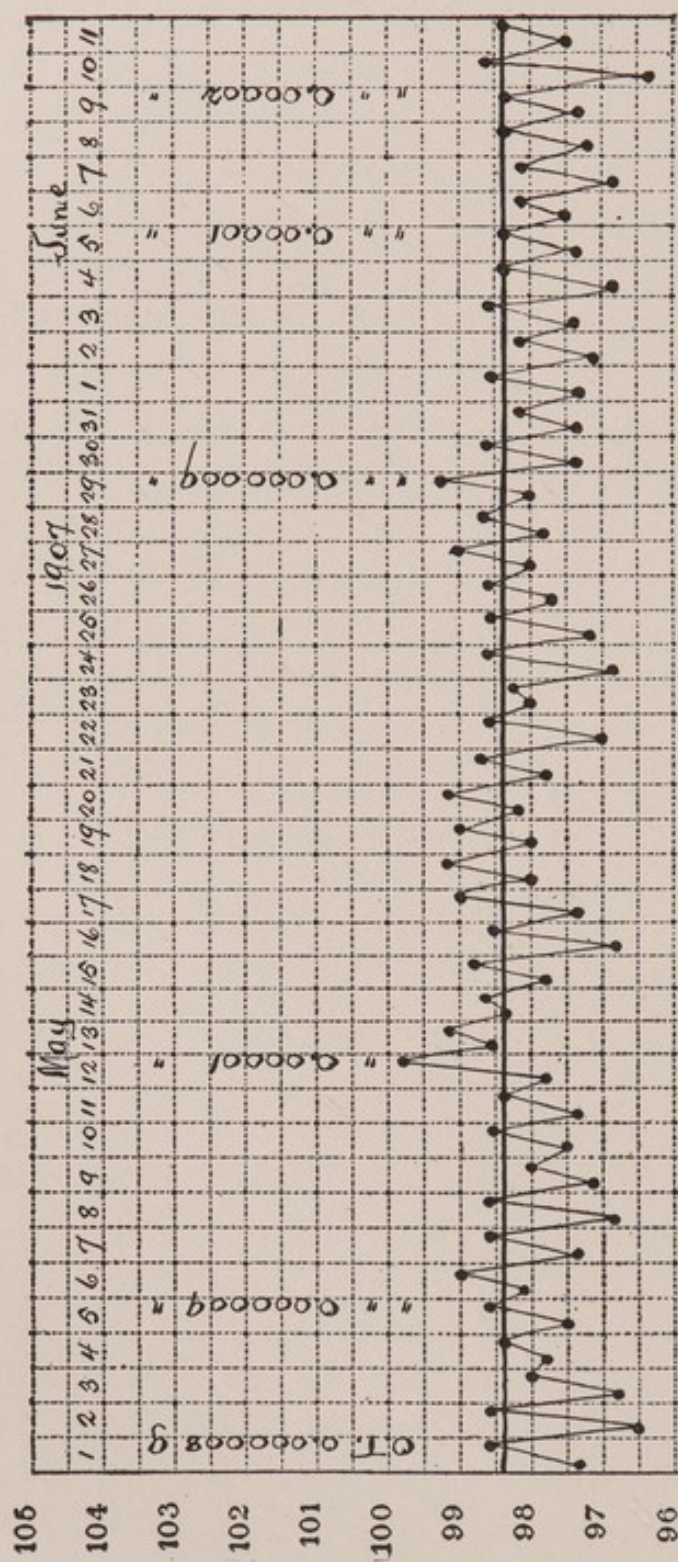


FIG. XXV.—CASE No. 1217. After the injection on May 5, patient had local pain and swelling. After omitting one dose he received a still higher dose followed by a prolonged reaction accompanied by marked constitutional symptoms for the first few days and a prolonged period of general malaise. On the 29th there is a slight reaction with constitutional symptoms to a smaller dose. No further reactions although the dose is steadily increased.

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lowed by 0.2 c. c. of the same solution, the ratio of increase will be much greater than while increasing doses of Solution VI were being used, for in this series there was always an arithmetical increase by 0.1 c. c. of VI. But, since 0.1 c. c. of V = 1.0 c. c. of VI, the difference between 0.1 c. c. of V and 0.2 c. c. of V is that between 1.0 c. c. and 2.0 c. c. of VI; that is, the increase in the dose suddenly becomes ten times as great as it has been heretofore. Of course, no one wishes intentionally to increase the tuberculin so suddenly. In fact, it would have occurred to no one to do so; and the reason that it is ever done is the solely accidental and mechanical one that for the convenience of making the solutions the decimal system was used. To avoid this sudden leap Béraneck's tuberculin is marketed in solutions of which each stronger one is only double, and not ten times the concentration of the next weaker.¹ However, the decimal system is less bulky and quite safe, if only certain precautions are taken.

If the patient is in the sensitive class it is well to repeat once or more often the first dose of each stronger solution as it is reached. And then, instead of proceeding to 0.2 c. c., only 0.15 c. c. may be given, thus bridging the gap. Or, in patients not so sensitive, a few leaps may be taken in the weaker solution, so as to test the patient's tolerance, and, if it is good, the first dose need not be repeated, and the next higher (or only half) be given at once. For example, the procedure may be of VI—0.1 c. c., 0.2, 0.3, 0.5, 0.7 c. c., followed by V—0.1, 0.15, 0.2, 0.3 c. c., etc.; or of VI—0.1, 0.2, 0.4, 0.7 c. c., followed by V—0.1, 0.2 c. c., etc.; or of VI—0.1, 0.2, 0.4, 0.8 c. c., followed by V—0.15, 0.3, 0.6, 0.9 c. c., etc.; or of VI—0.1, 0.3, 0.7 c. c., followed by V—0.15, 0.3 c. c., etc.

¹ Benker: Safe guide for the administration of tuberculin. *Interstate Med. Jour.*, 1911, xviii, 407.

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The following table illustrates the increase of dose in a patient who tolerates the tuberculin extremely well:

S. C., age 22. Phipps No. 7,874.
1911.

| | | | | |
|-----------|-------|-------------------|---------------------------|-----------------------------------------------------------|
| Sept. 19. | B. F. | 0.000,000,1 c. c. | T. below 99. | No local or general reaction. |
| " 22. | " | 0.000,000,3 | " T. below 99. | No reaction of any kind. |
| " 26. | " | 0.000,000,5 | " T. below 99. | No reaction of any kind. |
| " 29. | " | 0.000,000,8 | " T. to 99 ² . | Slight local swelling. |
| Oct. 3. | " | 0.000,001 | " T. below 99. | Slight local pain. Slight cough, with some pain in chest. |
| " 6. | " | 0.000,001 | " T. below 99. | No reaction of any kind. |
| " 10. | " | 0.000,005 | " T. below 99. | No reaction of any kind. |
| " 13. | " | 0.000,01 | " T. below 99. | No reaction of any kind. |
| " 17. | " | 0.000,03 | " T. below 99. | No reaction of any kind. |

etc.

Note that the slight reaction after dose of September 29th and October 3d caused a slowing, and finally a repetition, of the dosage, with consequent increased tolerance.

The following case illustrates that of the more usual patient who cannot take tuberculin quite as fast as the one just cited:

E. M., age 33. Phipps No. 5,024.
1909.

| | | | | |
|---------|-------|-------------------|---------------------------|---------------------------------------------------|
| Dec. 7. | B. F. | 0.000,000,1 c. c. | T. to 99. | No local or general reaction. |
| " 10. | " | 0.000,000,2 | " T. to 99. | No local or general reaction. |
| " 14. | " | 0.000,000,4 | " T. to 99. | No local or general reaction. Slight sore throat. |
| " 17. | " | 0.000,000,5 | " T. below 99. | No local or general reaction. |
| " 21. | " | 0.000,000,7 | " T. to 99. | No local or general reaction. |
| " 28. | " | 0.000,001 | " T. to 99 ⁶ . | No local or general reaction. Slight sore throat. |
| " 31. | " | 0.000,001,5 | " T. to 99 ² . | No local trouble. |
| 1910. | | | | |
| Jan. 4. | " | 0.000,003 | " T. to 99 ² . | No local trouble. |
| " 11. | " | 0.000,004 | " T. to 99. | No local trouble. |
| " 14. | " | 0.000,005 | " T. to 99. | No local trouble. |
| " 18. | " | 0.000,007 | " T. to 99 ² . | No local trouble. |
| " 21. | " | 0.000,008 | " T. below 99. | No local trouble. |
| " 25. | " | 0.000,009 | " T. below 99. | No local trouble. |
| " 28. | " | 0.000,01 | " T. below 99. | No local trouble. |

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E. M., age 33. Phipps No. 5,024.
1910.

| | | | | | | |
|------|-----|-------|-----------|------|--------------|-------------------|
| Feb. | 1. | B. F. | 0.000,015 | c.c. | T. to 99. | No local trouble. |
| " | 4. | " | 0.000,02 | " | T. below 99. | No local trouble. |
| " | 8. | " | 0.000,03 | " | T. to 99. | No local trouble. |
| " | 11. | " | 0.000,05 | " | T. below 99. | No local trouble. |
| " | 15. | " | 0.000,08 | " | T. to 99. | No local trouble. |
| " | 18. | " | 0.000,1 | " | T. below 99. | No local trouble. |
| " | 25. | " | 0.000,15 | " | T. below 99. | No local trouble. |

etc.

At Saranac the following scale was used for some time: 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 15, etc. Bandelier and Roepke used the following: for the small doses 1, 3, 6, 10, 15, 30, 60, etc. For the higher doses, 1.5, 2, 3, 5, 7, 10, 15, etc. Petruschky progresses more rapidly than Bandelier and Roepke, but the real stamp of rapidity is not so much the dose as the number of reactions that are met with. Bandelier and Roepke, if the reacting temperature is not greater than 100.4° F. (38° C.), do not consider it necessary to decrease the dose. Petruschky is even bolder. But Sahli and we ourselves would consider a reaction of 100.4° as decidedly to be avoided.

Pope of Saranac has worked out a series of logarithmic scales of dosage for the use of slow and rapid patients. These scales, if adhered to, would allow the doses of each patient to proceed by equal steps. We quote Brown:¹ "It is intended merely as a suggestion in controlling the dosage, which for each patient varies greatly, according to individual susceptibility, and is of use in giving any tuberculin, for all tuberculins are either in solution or suspension in fluids. This schema, computed by Pope, is based on a logarithmic scale, and is so arranged that in going from 0.1 to 1 c. c. of any solution two to twelve doses may be employed, while the rate of increase of dose in each case is always constant. The average patient, in the writer's experience, can take the sixth scale (six doses to each solu-

¹ Brown: In Klebs, Tuberculosis, p. 540.

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tion) without any danger of reaction, but some must go more slowly and a few, especially during a second course, may go more rapidly.

| Doses (Logarithmic Scale) | | | | | | | | | | |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 3.2 | 2.2 | 1.8 | 1.6 | 1.5 | 1.4 | 1.3 | 1.3 | 1.3 | 1.2 | 1.2 |
| 10 | 4.7 | 3.2 | 2.5 | 2.2 | 2.0 | 1.8 | 1.7 | 1.6 | 1.5 | 1.5 |
| | 10 | 5.6 | 4.0 | 3.2 | 2.7 | 2.4 | 2.2 | 2.0 | 1.8 | 1.8 |
| | | 10 | 6.3 | 4.7 | 3.7 | 3.2 | 2.8 | 2.5 | 2.3 | 2.2 |
| | | | 10 | 6.8 | 5.2 | 4.2 | 3.6 | 3.2 | 2.9 | 2.6 |
| | | | | 10 | 7.2 | 5.6 | 4.7 | 4.0 | 3.5 | 3.2 |
| | | | | | 10 | 7.5 | 6.0 | 5.0 | 4.3 | 3.8 |
| | | | | | | 10 | 7.7 | 6.3 | 5.3 | 4.7 |
| | | | | | | | 10 | 8.0 | 6.6 | 5.6 |
| | | | | | | | | 10 | 8.0 | 6.8 |
| | | | | | | | | | 10 | 8.3 |
| | | | | | | | | | | 10 " |

There is little advantage in the use of scales, however, as few patients will remain in any one system for any length of time, nor can we tell at the beginning of treatment where the patient best belongs.

There is much room for individualization in the choice of a scale, the patient himself always serving as a safe guide and corrector. At any sign of a reaction do not increase the dose, but repeat or even decrease it, or even increase the interval between doses. If a definite reaction should occur, the course to be followed depends upon the intensity of the reaction. If it has been only slight, it may be enough simply to repeat the dose. If severe, the dose should be considerably decreased below the one that elicited the reaction, and for a while the usual interval may be lengthened. If the reaction has taken a considerable time to subside—if it has lasted more than 24 to 48 hours—it is well to rest the patient for a week or more before resuming treatment. As a general rule, do not resume treatment until the disturbance caused by the troublesome

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dose has disappeared, and if the disturbance has been at all severe wait even longer. Figures XXV to XXX show sensitive patients. In XXV, XXVI, XXVII the sensitiveness is finally overcome. In XXVIII, XXIX, XXX the difficulty is greater. There are two cases that suggest some difficulty in increasing the dose.

Dispensary No. 2,162. Mamie F., white female, age 19, single. Onset of illness in August, 1907. Was run down, and during a vacation "caught cold." Had cough, weakness and loss of appetite. Came to Dispensary November 9, 1907, complaining of severe cough and weakness. Family history negative and no history of exposure. Had lost 9 pounds.

Examination.—Temperature 100° F., pulse 130, respiration 22, weight 109 lbs. Pale, frail girl; eyes sunken; poorly nourished.

Lungs.—Right: Note impaired to third rib and behind to angle of scapula; breath sounds diminished in intensity with tubular quality above and below clavicle and in supraspinous fossa. Moist râles on quiet breathing to second rib; after coughing to fourth rib, and behind to angle of scapula. Left: Note impaired less markedly than on right above and below clavicle and in supraspinous fossa; more marked dulness at extreme base behind. Breath sounds harsh at apex and at base. Few fine moist râles above and below clavicle and at base behind. Mucopurulent sputum with tubercle bacilli.

On January 3, 1908, O. T. begun with injection of 0.000,000,1 gm. Dose was gradually raised, and several slight reactions occurred in the hundredths of a milligram, necessitating a return to 0.000,005 gm. on June 26, 1908. Dose again raised until, on October 13, she received 0.000,4 gm.

1908.

| | | | | |
|------|-----|-------|--------------|--------------------------------------------------------------------------------------------------------|
| Oct. | 20. | O. T. | 0.000,5 gm.; | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 23. | " | 0.000,6 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 27. | " | 0.000,8 " | no fever; marked local swelling, although patient made no complaint of it; no constitutional symptoms. |
| " | 30. | " | 0.001 " | temperature to 101.6° F.; some cough and general malaise; no local swelling. |
| Nov. | 13. | " | 0.000,1 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 17. | " | 0.000,2 " | no fever; no local pain or swelling; no constitutional symptoms. |

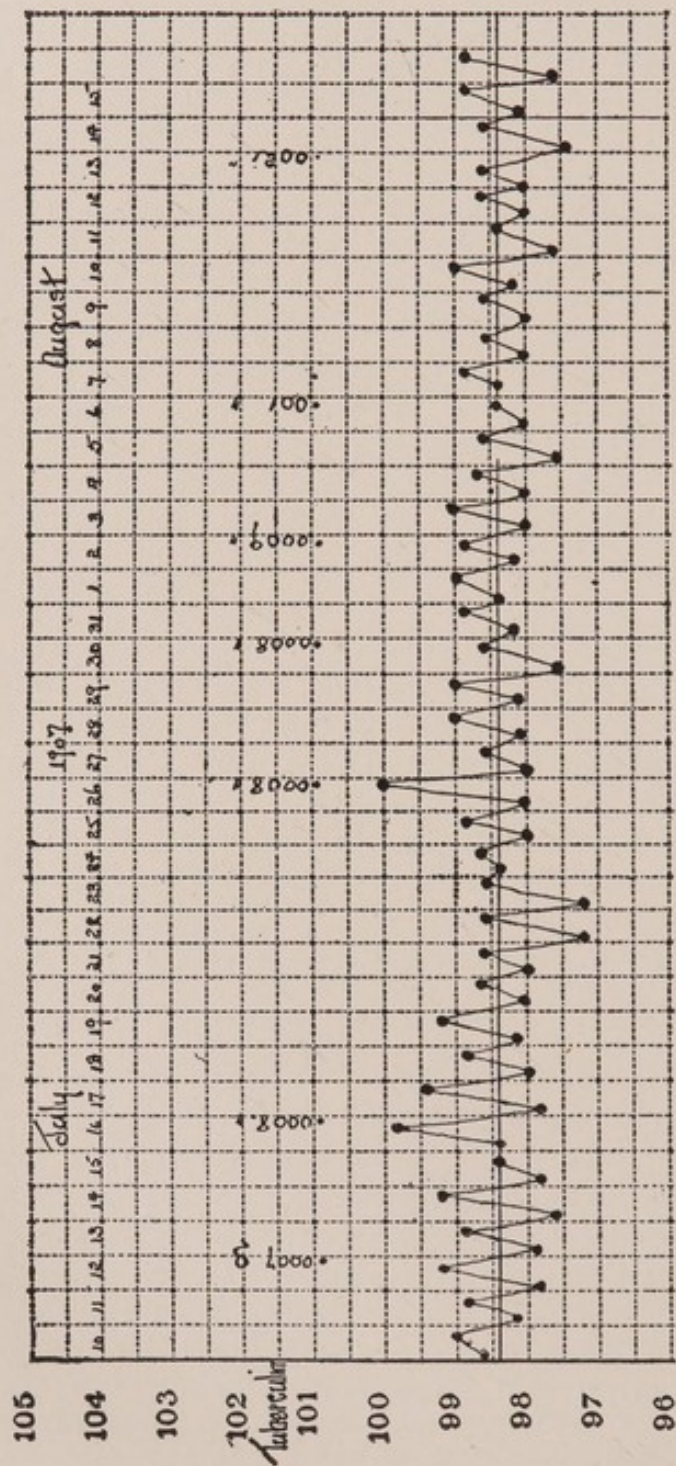


FIG. XXVI.—CASE No. 830. On July 16 there is a mild reaction and on the 26th another reaction when the same dose is repeated after a pause of 10 days. There are no further reactions although the dose is steadily increased.

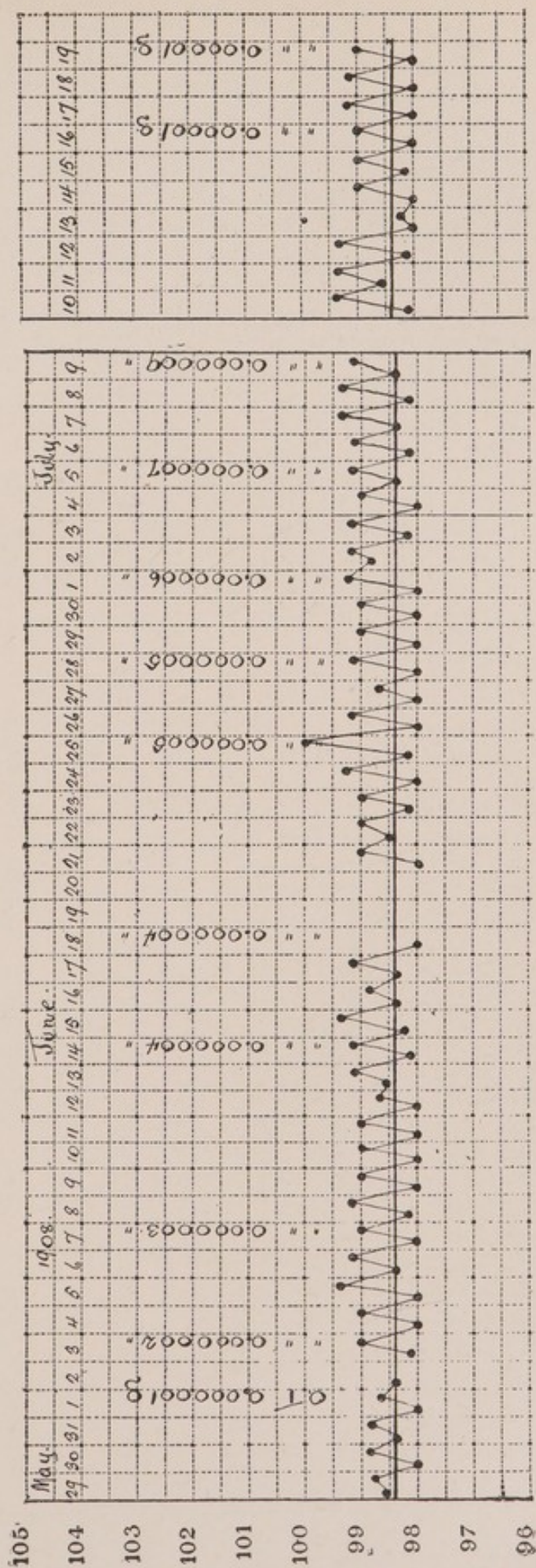


FIG. XXVII.—CASE No. 1542. This chart shows a number of slight reactions to small doses. The dose is gradually increased and tolerance acquired.

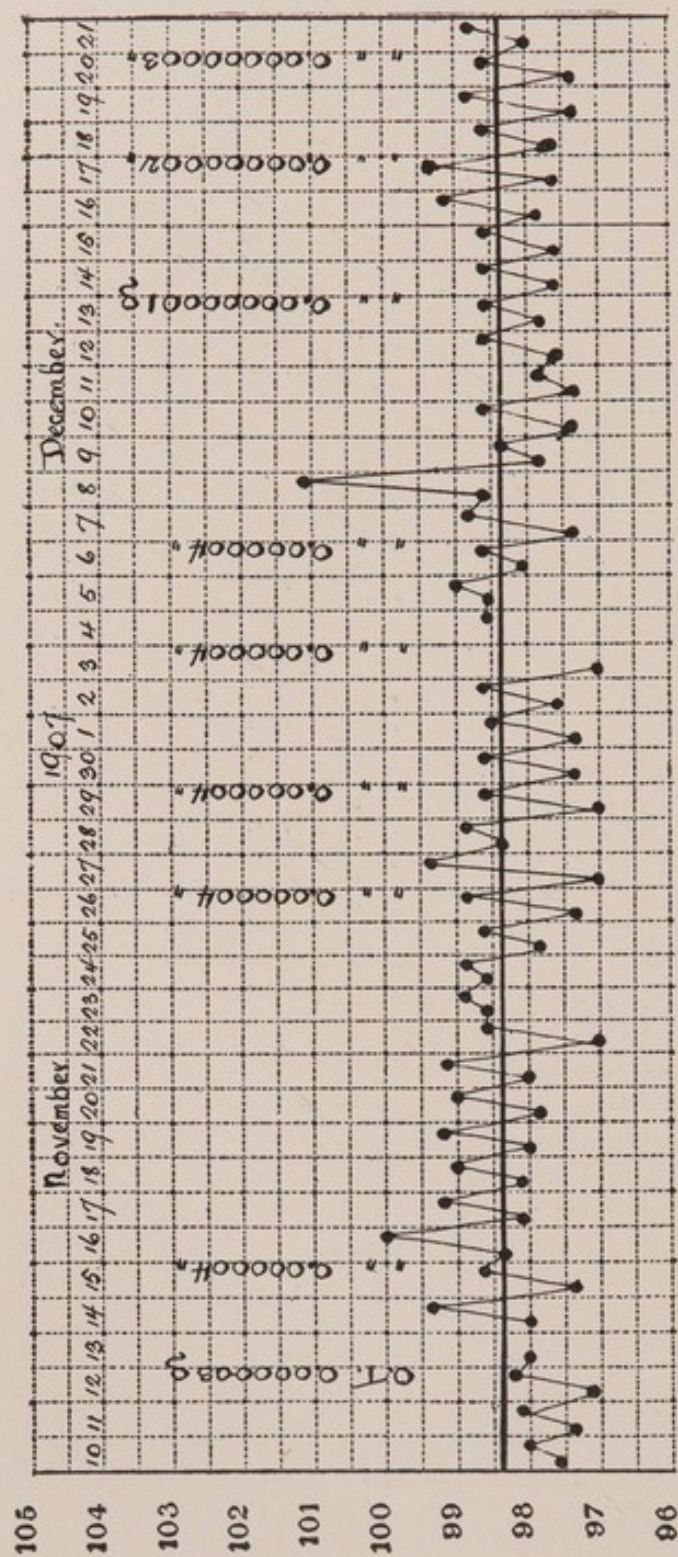


FIG. XXVIII.—Case No. 1336. This chart shows very well a number of slight reactions to 0.000,004 gm. O. T. with a severe reaction after the fifth dose. There had been local pain and swelling after several of the preceding doses.

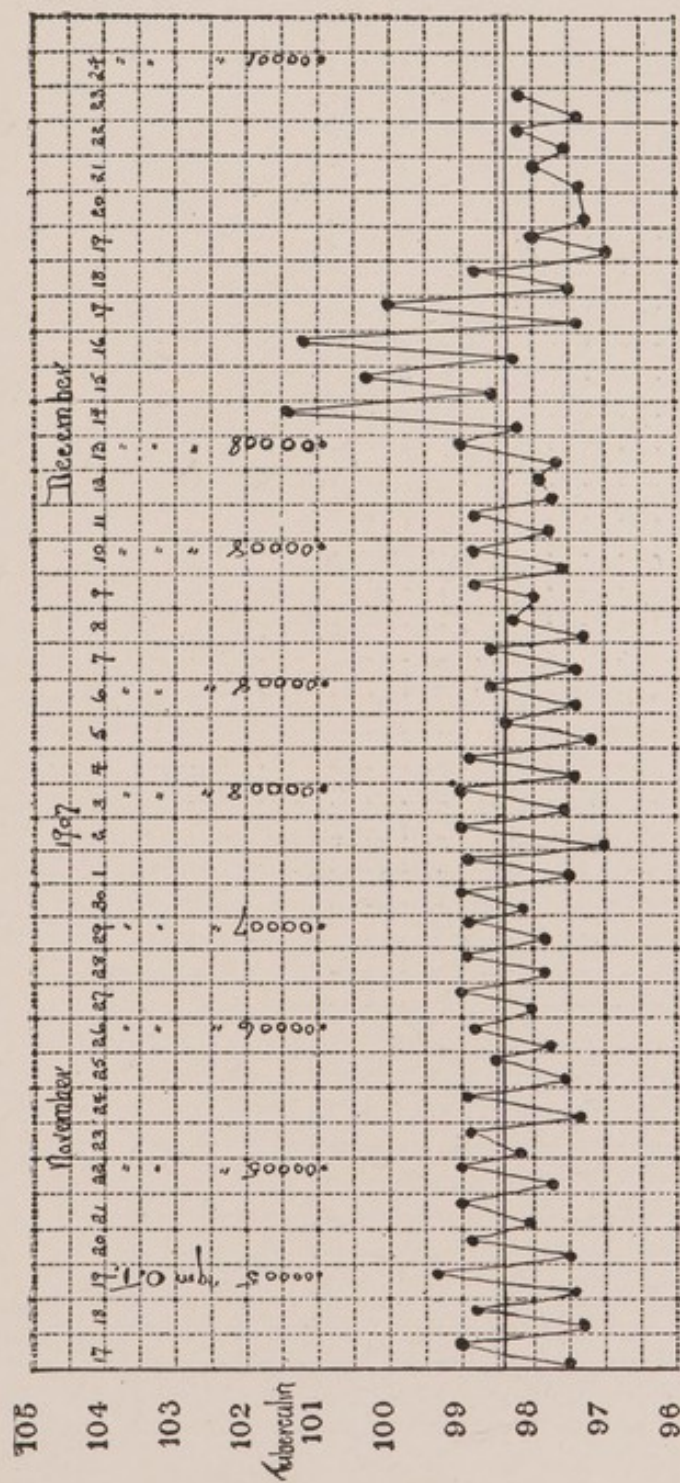


FIG. XXIX.—CASE No. 1811. On December 14 there is a characteristic reaction following the fourth dose of 0.000,08 gm. after sensitiveness to previous reactions had appeared at site of injections.

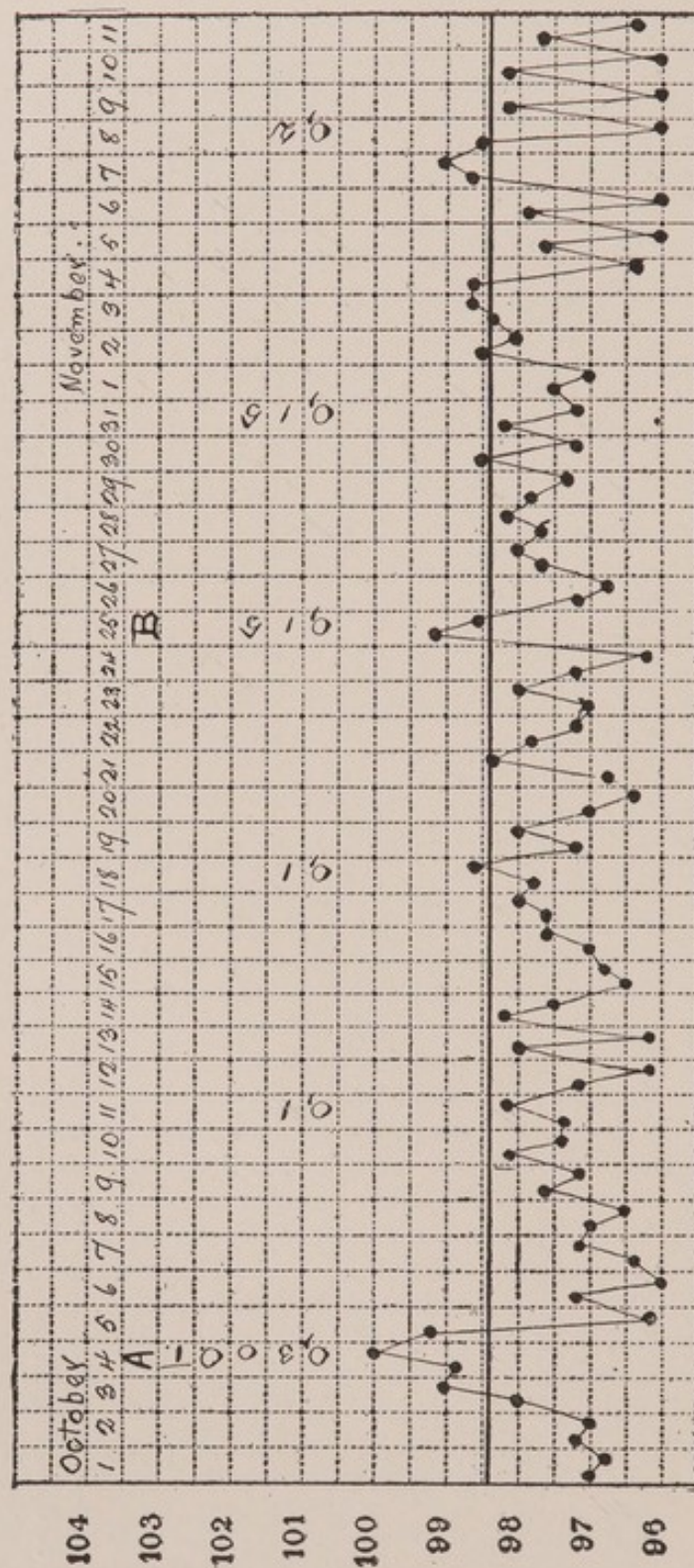


FIG. XXX (a).—Case No. 1151._j

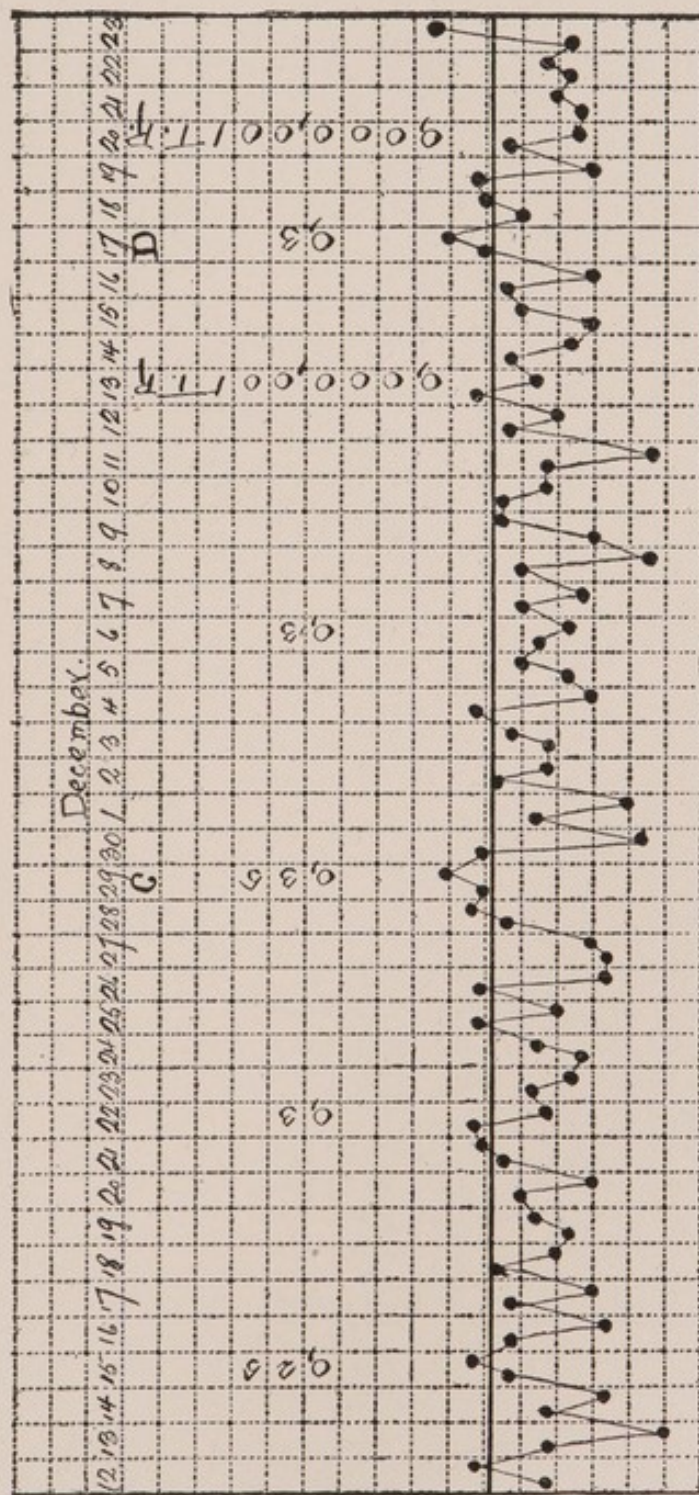


Fig. XXX (b). —Case No. 1151.

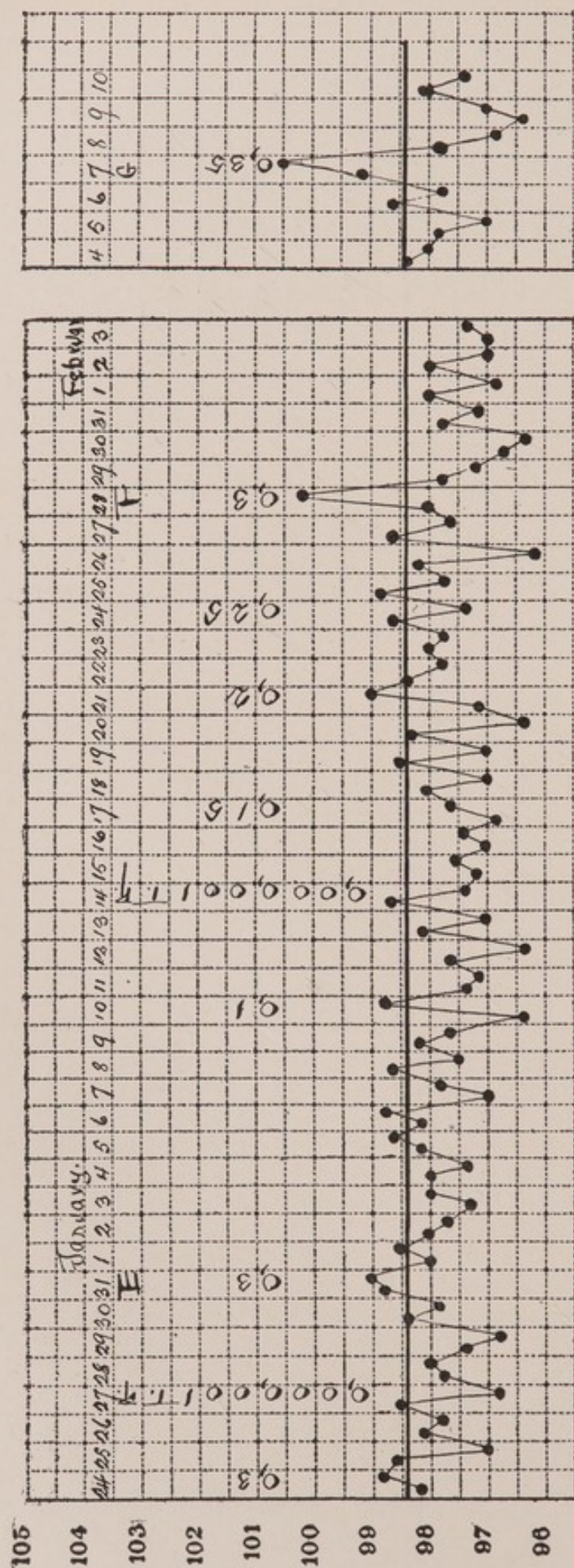


FIG. XXX (c).—CASE No. 1151. In this case 0.3 gm. is approached three times, but is not passed successfully. At *A* there is a reaction to 0.3 gm. The dose is then reduced but at *B* there is a mild reaction to 0.15 gm. Upon the repetition of this dose there is no reaction. At *C* there is a mild reaction to 0.35 gm. and at *D* another reaction to 0.30 gm. Each reaction being accompanied by constitutional symptoms. At *E* and at *F* there are again definite reactions to 0.3 gm. and at *G* a reaction to 0.35 gm. These last reactions although the temperature was higher were accompanied by fewer constitutional symptoms than the preceding reactions.

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1908.

| | | | | |
|------|-----|-------|-------------|-------------------------------------------------------------------------------|
| Nov. | 20. | O. T. | 0.000,3 gm. | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 27. | " | 0.000,4 " | no fever; no local pain or swelling; no constitutional symptoms. |
| Dec. | 1. | " | 0.000,5 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 4. | " | 0.000,6 " | no fever; marked local pain and swelling; no constitutional symptoms. |
| " | 8. | " | 0.000,8 " | temperature to 99° F.; no local pain or swelling; no constitutional symptoms. |
| " | 11. | " | 0.000,8 " | no fever; some local tenderness; no constitutional symptoms. |
| " | 15. | " | 0.000,8 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 22. | " | 0.000,8 " | temperature to 99° F.; no local pain or swelling; no constitutional symptoms. |
| " | 29. | " | 0.001 " | no fever; no local pain or swelling; no constitutional symptoms. |

1909.

| | | | | |
|------|-----|---|-----------|---------------------------------------------------------------------------------------|
| Jan. | 5. | " | 0.002 " | temperature to 99° F.; no local pain or swelling; no constitutional symptoms. |
| " | 8. | " | 0.002 " | temperature to 99° F.; no local pain or swelling; no constitutional symptoms. |
| " | 12. | " | 0.002 " | temperature to 99° F.; marked local swelling and redness; no constitutional symptoms. |
| " | 15. | " | 0.001 " | temperature to 99° F.; slight local swelling and redness; no constitutional symptoms. |
| " | 19. | " | 0.001 " | temperature to 99° F.; no local pain or swelling; no constitutional symptoms. |
| " | 22. | " | 0.001 " | caught a "cold"; temperature on 25th 99.4° F. |
| Feb. | 2. | " | 0.001 " | temperature to 99° F.; no local pain or swelling; no constitutional symptoms. |
| " | 5. | " | 0.001 " | temperature to 99° F.; moderate local swelling; indigestion. |
| " | 9. | " | 0.001 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 12. | " | 0.001,5 " | temperature to 99° F., no local pain or swelling; no constitutional symptoms. |
| " | 23. | " | 0.001 " | temperature to 99° F.; no local pain or swelling; no constitutional symptoms. |

THE USE OF TUBERCULIN IN TREATMENT

| | | | | |
|-------|-----|-------|---------|--------------------------------------------------------------------------------------------------|
| 1909. | | | | |
| Mar. | 1. | O. T. | 0.001 | gm.; no fever; no local swelling; no constitutional symptoms. |
| " | 5. | " | 0.001,5 | " temperature to 99.2° F.; no local pain or swelling; no constitutional symptoms. |
| " | 9. | " | 0.001,5 | " no fever; no local pain or swelling; no constitutional symptoms. |
| " | 12. | " | 0.002 | " temperature to 99.4° F.; no local pain or swelling; no constitutional symptoms. |
| " | 19. | " | 0.002 | " temperature to 99.4° F.; no local pain or swelling; no constitutional symptoms. |
| " | 23. | " | 0.001 | " no fever; no local pain or swelling; no constitutional symptoms. |
| " | 26. | " | 0.001,5 | " no fever; swelling at site of injection and of previous injection; no constitutional symptoms. |
| " | 30. | " | 0.001 | " no fever; no local pain or swelling; no constitutional symptoms. |
| April | 2. | " | 0.001,5 | " temperature to 99.2° F.; some local swelling; no constitutional symptoms. |
| " | 6. | " | 0.001 | " temperature to 99.8° F.; no local pain or swelling; no constitutional symptoms. |

From beginning of treatment to February 12, 1909, patient gained 17 lbs.; but during period of hypersensitiveness, with many slight reactions, she lost 4¾ lbs. Patient's general condition has greatly improved, and nearly all symptoms have subsided. Sputum on June 9, 1908, was negative, and she had no sputum since then. Râles have disappeared on the left side, and are less numerous, and not so extensive on the right.

By selecting a dose just short of the one to which the patient reacts and repeating this dose indefinitely, or by returning to a smaller dose and gradually increasing, we are usually able to overcome this hypersensitiveness.

The following case is illustrative:

Dispensary No. 3,127. Maud R., white female, age 28, single. Has had cough, always worse in winter, for three years. Two years ago had four or five hemoptyses; maternal grandmother and one brother and one sister have died of pulmonary tuberculosis. Patient lived at home while brother and sister were sick. Came to dispensary July 21, 1908, complaining of cough and expectoration.

Examination.—Temperature 98.8° F., pulse 92, respiration 16, weight 115½ lbs. Fairly well nourished, good color, does not look ill.

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Lungs.—Right: Note impaired above and below clavicle and behind to fourth dorsal spine; breath sounds above clavicle tubular, below harsh and interrupted, in supraspinous fossa rather suppressed with tubular quality; after cough a few moist râles above and below clavicle. Left: Note a little impaired above clavicle and in supraspinous fossa; breath sounds rather harsh; few fine râles above clavicle after cough. Cutaneous and conjunctival reactions positive: No tubercle bacilli found in sputum.

Tuberculin treatment begun on August 18, 1908, with 0.000,000,1 gm. bouillon filtrate. Dose was then uneventfully raised until October 27, 1908.

1908.

| | | | | |
|------|-----|-------|---------------|-------------------------------------------------------------------------------|
| Oct. | 27. | B. F. | 0.000,004 gm. | temperature to 99° F.; marked local swelling; no constitutional symptoms. |
| Nov. | 6. | " | 0.000,001 " | temperature to 99° F.; no local pain or swelling; no constitutional symptoms. |
| " | 10. | " | 0.000,001 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 13. | " | 0.000,002 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 17. | " | 0.000,003 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 20. | " | 0.000,004 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 24. | " | 0.000,005 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 27. | " | 0.000,006 " | no fever; no local pain or swelling; no constitutional symptoms. |
| Dec. | 1. | " | 0.000,008 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 4. | " | 0.000,01 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 8. | " | 0.000,015 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 11. | " | 0.000,02 " | no fever; some local soreness and swelling; no constitutional symptoms. |
| " | 15. | " | 0.000,02 " | no fever; slight local soreness; no constitutional symptoms. |
| " | 18. | " | 0.000,02 " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 22. | " | 0.000,03 " | no fever; no local pain or swelling; no constitutional symptoms. |

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1908.

Dec. 29. B. F. 0.000,04 gm.; temperature to 99° F.; slight local soreness; no constitutional symptoms.

1909.

| | | | | | |
|------|-----|---|----------|---|----------------------------------------------------------------------------------|
| Jan. | 2. | " | 0.000,04 | " | temperature to 99° F.; no local pain or swelling; "biliousness." |
| " | 5. | " | 0.000,05 | " | temperature to 99° F.; slight soreness and swelling; no constitutional symptoms. |
| " | 8. | " | 0.000,05 | " | no fever; slight local pain; no constitutional symptoms. |
| " | 12. | " | 0.000,07 | " | no fever; marked local pain and swelling; no constitutional symptoms. |
| " | 15. | " | 0.000,06 | " | temperature to 99° F.; slight local pain; no constitutional symptoms. |
| " | 19. | " | 0.000,05 | " | temperature to 99.8° F.; no local pain or swelling; no constitutional symptoms. |
| " | 22. | " | 0.000,05 | " | temperature to 99° F.; no local pain or swelling; no constitutional symptoms. |
| " | 26. | " | 0.000,07 | " | no fever; local pain and swelling; no constitutional symptoms. |
| " | 29. | " | 0.000,07 | " | temperature to 99° F.; local pain and swelling; no constitutional symptoms. |
| Feb. | 2. | " | 0.000,06 | " | temperature to 98.8° F.; local pain and swelling; no constitutional symptoms. |
| " | 5. | " | 0.000,06 | " | no fever; slight local pain; no constitutional symptoms. |
| " | 9. | " | 0.000,07 | " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 12. | " | 0.000,08 | " | temperature to 99.4° F.; local pain and swelling; headache and general malaise. |
| " | 23. | " | 0.000,01 | " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 26. | " | 0.000,02 | " | no fever; no local pain or swelling; no constitutional symptoms. |
| Mar. | 2. | " | 0.000,03 | " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 5. | " | 0.000,04 | " | no fever; no local pain or swelling; no constitutional symptoms. |

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1909.

| | | | | | |
|-------|-----|-------|----------|------|--------------------------------------------------------------------------------------|
| Mar. | 9. | B. F. | 0.000,05 | gm.; | temperature to 98.8° F.; slight local pain and swelling; no constitutional symptoms. |
| " | 12. | " | 0.000,05 | " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 23. | " | 0.000,07 | " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 26. | " | 0.000,09 | " | temperature to 99° F.; no local pain or swelling; no constitutional symptoms. |
| " | 30. | " | 0.000,1 | " | no fever; no local pain or swelling; no constitutional symptoms. |
| April | 2. | " | 0.000,2 | " | temperature to 99° F.; no local pain or swelling; no constitutional symptoms. |
| " | 6. | " | 0.000,4 | " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 13. | " | 0.000,7 | " | no fever; no local pain or swelling; no constitutional symptoms. |
| " | 16. | " | 0.001 | " | no fever; no local pain or swelling; no constitutional symptoms. |

Patient's general condition has improved very much. She now has no symptoms and has gained 26½ lbs. The râles have disappeared.

Attempts have been made to find other than the ordinary clinical guides for arranging the successive doses. The most ambitious have been those of Wright. He arranges the interval by an estimate of the opsonins, and does not increase the dose at all, but continues giving the small dose with which he started. Others have attempted, however, to use the opsonins as a guide to the increase of the dose. There are serious objections, however, to the study of the opsonins for this purpose, on account of their wide fluctuations in tuberculosis.¹ It has not been found that the blood,² sputum, urine or blood-pressure are of any help. Morland³ reports intracellular tubercle bacilli

¹ Moss: Studies on opsonins. Johns Hopkins Hosp. Bull., 1907, xviii, 237.

² Meakins: An experimental study of the phagocytic immunity produced by tuberculin. Canadian Med. Assn. Jour., 1911, p. 1141.

³ Morland: Ueber die klinische Bedeutung der Opsonine. Inaugural dissertation, Samaden, 1908.

THE USE OF TUBERCULIN IN TREATMENT

in the sputum during the positive phase, but this is of doubtful value, and, moreover, inapplicable in many cases.

Knowing the initial dose, the interval between doses, and the rate of increase of the dose, the next question is, when shall the tuberculin be stopped, or what is the maximum dose? For the determination of the maximum dose we have no strict criterion. An empirical maximum is in common use, which has for its justification perhaps more of convenience than anything else. The conventional maximum is 1 gram of B. F. or O. T., and 2 grams of T. R. or B. E. Perhaps this is so, because in the time usually allotted to a sanatorium patient this dose is rarely exceeded. Or, in private practice, it is about as long as a patient will continuously submit to rigorous discipline. This dose is attained usually in about six months, though perhaps at three months, and often not in a year. Many clinicians maintain that if more than one gram of O. T. or B. F. is attempted the patient will begin to lose weight and to feel less vigorous, even without the occurrence of an actual reaction. This is said to be due to "Gift-belästigung," or poisoning. That doses higher than one gram are intrinsically harmful is not at all likely. Individuals have safely taken more. The question is open for experimentation, and we do not see why any one who thinks that higher doses should be given should refrain from giving them, if he finds no contraindication in the status of the patient before him.

Denys has given as much as 10 c. c. of B. F. subcutaneously, and 2.5 c. c. intravenously, and no doubt the conventional maximum dosage of other varieties of tuberculin could be much exceeded, without harming individual cases. After all, the conventional maximum means simply that the average patient does not do well if the dosage is pushed farther. In brief, the conventional maximum is merely the average patient's optimum dose. And the inference we

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must draw is that the maximum dose for any patient should not be pushed beyond this optimum; nor need it stop before that optimum, no matter how large the dose is. Still, it is well to know for each tuberculin the sum total of clinical experience as to where it has been found that it is, as a rule, best to stop. By stating that the conventional maximum dose is merely the average optimum dose we do not mean that the patient derives greater benefit from the optimum dose than he has derived from any of the antecedent doses. The dose is an optimum dose merely in the sense that to go higher would do harm. But, in its own season, each of the antecedent doses was really an optimum dose. Each of these doses was about as large a dose as the patient could then tolerate, and was stimulating the focus of the disease as much as it should have been stimulated. A patient whose optimum dose is small may be reaping as many benefits from that dose as another patient from a much higher dose. (But it is true that most of the patients who cannot go beyond a very small dose do not fare well.) It is the constant stimulation that is therapeutically efficient, so that the doses are raised, not because we wish to attain large doses, but because, as a rule, in order to maintain the stimulation, we are forced to give larger and larger doses. When the patient's sensitiveness is such that we are not forced to huge doses in order to maintain a constant stimulation, we need not feel that we are in a deplorable position.

We are now confronted by the question as to what the procedure is when the maximum dose has been attained.

Duration of Treatment.—There are two contrasted courses. One is to continue the maximum dose at intervals of one or more weeks, indefinitely. The other is to discontinue the treatment for a number of months, and then to resume treatment, of course with a small dose, since the patient's immunity to tuberculin has by that time prob-

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ably been lost. Either plan may have the advantage of convenience in individual cases. For the continuous, uninterrupted plan it may be said that if it is of advantage to the patient to be in a state of high immunity against tuberculin there is reason for maintaining and not interrupting that state.

The other view is that, in the long run, more of an immunity is maintained by not stimulating the system continually. Also, since the greatest benefits of tuberculin therapy are derived from the constant, though mild, focal stimulation, some argue that it is well to allow the immunity to diminish now and then so that the focal effects may be obtained without the necessity of using extremely high doses. Probably the solution of this controversy, too, lies in individualization. We know of patients who can take the maximum dose for a long time without any ill effects. We know, too, of cases in which we found it advisable to interrupt the course. One thing is objectively certain: as judged by the cutaneous test, some patients, after discontinuing tuberculin treatment, retain an immunity much longer than others. However this fact may be employed in the argument, it certainly demonstrates the variability of individual patients. We do not see any reason, therefore, for not maintaining the treatment where it does no demonstrable harm, for, after all, the foundation of tuberculin therapy is at present empirical. But if the course is not interrupted, and the large doses are given continually, it is well to increase the interval to such an extent that extremely mild local reactions are now and then obtained.

Bandelier and Roepke give the maximum dose at 8 to 10 to 14 days' interval, as long as it seems beneficial. Brown, too, gives the maximum dose as long as the patient feels its stimulating effects. Weddy-Poenicke recommends a 3—4—8-week interval. For T. R., Bandelier and

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Roepke used 4 to 8-week pauses. Petruschky reaches a maximum dose of about 50 to 100 mg. in 2 to 3 months. He then pauses 3 to 4 months and gives a second course, and so on for two years. This method is known as the "stage-cure." Pickert,¹ on the basis of antibody studies, recommends a 14-day interval for the maximum dose. Jochmann advises interrupting the treatment when the skin test becomes negative, which he says is at 300-500 mg. O. T. However, such patients may, in our experience, still have positive sputum and a progressive lesion, causing symptoms. He recommends resumption of treatment when the skin test becomes again positive. Petruschky, Bandelier and Roepke, and Brown believe in applying the subcutaneous test in order to determine the necessity for another course of treatment. We see no advantage in applying this subcutaneous test, however, and possibly some danger from the focal reaction. Its purpose seems to be mainly to test the sensibility of the patient and thus to enable us, in certain cases, to begin the course with a rather large dose. However, the cutaneous or intracutaneous test accomplishes the same purpose, with much less trouble to the patient or physician. As patients on their second course usually take tuberculin rapidly, very little is lost even by beginning with a smaller dose than the patient would tolerate.

What has been said about the conventional maximum dose applies equally to any other dose beyond which it does not seem advantageous to go. For some patients the maximum dose is very low. By this we mean that giving more than this low dose causes disturbance. The optimum dose—the dose beyond which damage is done—should then be regarded as the maximum dose for that patient. The differ-

¹Pickert: Ueber das gesetzmässige Auftreten von Tuberkulin-Antikörpern im Laufe der spezifischen Behandlung und seine Bedeutung für die Therapie. Deutsch. med. Wchnschl., 1909, xxxv, 1514.

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ence between the conventional maximum dose and the optimum dose is that the former may be even less than what for that case is optimal, while anything greater than the optimum dose is harmful.

If the patient's intolerance is such that reactions persist for weeks after very small doses it is best to discontinue tuberculin, at least temporarily, until the patient's general condition is improved. But not every initial sensitiveness should lead to an interruption. A few weeks of low dosage persisted in in many cases allow finally of rapid progress.

Since the advent of the external tuberculin reactions (skin and eye) persistent attempts have been made to correlate the relation between the amount of tuberculin which on subcutaneous introduction elicits a reaction and that which cutaneously produces a reaction. What relation is there between the amount of tuberculin which gives a cutaneous reaction by the v. Pirquet method, for instance, and the dose for a reaction subcutaneously?¹ That the relation is not constant is certain. That it does exist is probable. White and Van Norman² (see Section I, p. 182) have attempted to regulate the dose by the size of the skin-reaction. Similar work has been done by Ellermann and Erlandsen.³ (See Section I, p. 180.) We ourselves are studying the intracutaneous reaction with reference to this problem. A preliminary survey of our data shows, apparently, no correlation between the size of the subcutaneous dose causing a local reaction and the intensity of the intracutaneous reaction. Moreover, in some patients, the intracutaneous test will become negative, although the dose of

¹ Saathof: Der persönliche Faktor in der Tuberkulinbehandlung. München. med. Wehnschr., 1910, lvii, 1738.

² White and Van Norman: The determination of individual dosage in tuberculin therapy. Arch. Int. Med., 1912, ix, 114.

³ Ellermann u. Erlandsen: Ueber quantitative Ausführung der kutanen Tuberkulinreaktion und über die klinische Bedeutung des Tuberkulintiters. Deutsch. med. Wehnschr., 1909, xxxv, 436.

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tuberculin administered subcutaneously has not reached nearly the level of that administered to others, in whom the intracutaneous test persists in remaining positive. If the problem is solved, we will have a method for determining in each patient the initial dose and other doses. The work of Ditthorn and Schultz¹ indicates anew the complexity of the question.

In connection with the use of the local reaction as a guide to the dosage, it has been noted that some cutaneous areas are more sensitive than others. Although some workers administer the tuberculin into the arm, we have not rarely found that in this region extremely severe local reactions occur, which do not appear with the same dose injected into the back. In one instance the local reactions in the arm were so huge as to prevent the continuation of treatment, had we not had recourse to the back, where no trouble was experienced in spite of progressively large doses.

The technique of the subcutaneous method of administration has been described. We must warn against the policy of injecting deep into the muscle, when using tuberculin therapeutically. This has been advised, in order to avoid the pain and inconvenience of local reactions. However, as it is exactly these reactions that we must be aware of, in order to use tuberculin with safety, we must consider the advice more harmful than unnecessary. In fact, care should be taken that the mouth of the needle faces the skin (as in making the intracutaneous test) so that the local reaction, if any, should be obvious. There is some difference of opinion as to the best time of the day for the administration of the therapeutic dose. For the morning it is argued that it will prevent the overlooking of slight febrile reactions that might occur at night if the dose were given

¹ Ditthorn u. Schultz: Versuche über die Einwirkung der Leberautolyse auf Tuberkulin. Deutsch. med. Wchnschr., 1911, xxxvii, 1695.

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in the afternoon. On the other hand, it is contended that the rest at night would tend to prevent such reactions as might occur with the patient up and about. Brown is in favor of the afternoon, because it affords an opportunity for omitting the dose, in case there is an accidental rise of temperature that day.

It is not essential that the patient rest for a few hours after the dose is administered. Many of the Phipps Dispensary patients engage in active work immediately before and after the dose is given to them. It is, however, true that in a sanatorium, where such rest can be enforced, the dosage may be increased with greater rapidity than in an ambulant clinic.

At the Phipps Dispensary it has been customary for each patient to be given a record book in which he enters as many data as his intelligence permits. This book is adopted from the one used by Brown at the Adirondack Cottage Sanitarium. The accompanying sheet (page 343) is a specimen page.

On the inside of the cover the following directions are printed:

INSTRUCTIONS

Now that you are to begin to take tuberculin it is important that you pay the greatest attention to keeping this record carefully and conscientiously. Whether we increase or decrease the amount of tuberculin you are receiving will depend entirely upon how you have stood the preceding dose, and the only way we can judge of this is from the record you keep. Your improvement depends, then, to a large extent upon the faithfulness with which you keep your record. Never put down a temperature unless you are sure of it, and never make any entry until you are sure that you understand the book.

Each page in this book will keep your record for a week.

As you see, there are seven columns. Put the date at the top of the column, and make a note after each symptom in the space immediately opposite it. You fill in each space every day, except the "tuberculin" space, which the doctor will fill in. After each symptom if you have it make a + mark. If you haven't it

| | | | | | | | |
|--------------------------|--|--|--|--|--|--|--|
| DATE: | | | | | | | |
| TEMPERATURE - - 8 A. M. | | | | | | | |
| 12 N. | | | | | | | |
| 4 P. M. | | | | | | | |
| 8 P. M. | | | | | | | |
| PULSE - - - - 8 A. M. | | | | | | | |
| 12 N. | | | | | | | |
| 4 P. M. | | | | | | | |
| 8 P. M. | | | | | | | |
| WEIGHT: | | | | | | | |
| TUBERCULIN: Dose | | | | | | | |
| PLACE OF INJECTION: Pain | | | | | | | |
| Swelling | | | | | | | |
| Enlarged Glands | | | | | | | |
| SYMPTOMS: Appetite | | | | | | | |
| Digestion | | | | | | | |
| Nausea | | | | | | | |
| Vomiting | | | | | | | |
| Headache | | | | | | | |
| Chilliness | | | | | | | |
| Pain in Joints | | | | | | | |
| Sleep | | | | | | | |
| Nervousness | | | | | | | |
| STRENGTH: As usual | | | | | | | |
| Increased | | | | | | | |
| Decreased | | | | | | | |
| COUGH: As usual | | | | | | | |
| Increased | | | | | | | |
| Decreased | | | | | | | |
| SPUTUM As usual | | | | | | | |
| Increased | | | | | | | |
| Decreased | | | | | | | |
| Blood in Sputum | | | | | | | |
| Pain in Chest | | | | | | | |
| Shortness of Breath | | | | | | | |
| REST: In Bed | | | | | | | |
| Sitting Down | | | | | | | |
| Exercise | | | | | | | |
| In Open Air | | | | | | | |
| DIET: Milk | | | | | | | |
| Eggs | | | | | | | |
| Oil | | | | | | | |
| Total gain in Weight | | | | | | | |

THE USE OF TUBERCULIN IN TREATMENT

make an O. After "appetite," "digestion," "sleep," write "good" or "poor," as may suit the case. Under the heading "rest" write how many hours spent in bed, how many in resting in a chair. In filling in the number of hours spent in the open air include those spent in bed if you sleep on a porch or with your windows out. Under "diet" put down the number of pints of milk, the number of eggs and the number of tablespoonfuls of oil. If you have any symptom, no matter how trivial it may seem to you, which is not in this book, tell the doctor about it at your next visit.

Other routes than the subcutaneous one have been employed, but they all have serious objections and need but little more than enumeration.

The Oral Route.—It has been shown that tuberculin reactions may be caused by tuberculin taken by mouth. Calmette and Guérin¹ have vaccinated calves by feeding them on tuberculous milk. Pfeiffer and Trunk, Levene, Baldwin have shown that the tuberculin is acted on in the digestive tract. But if the digestive enzymes weaken the tuberculin they apparently do not completely deprive it of its specific power. However, the amount of tuberculin that must be swallowed in order to produce a reaction is not susceptible of nearly as exact determination as when the dose is given subcutaneously. So much depends, apparently, upon the state of digestion and upon the state of the digestive tract.² And again, owing to the irregularity of absorption, much tuberculin may be absorbed suddenly, and cause unexpected reactions. Freymuth,³ father and son, neutralized the gastric juice with sodium bicarbonate before giving the tuberculin. But Huhs,⁴ who reacted after

¹ Calmette et Guérin: Contribution à l'étude de la vaccination des bovidés contre la tuberculose par les voies digestives. Ann. de l'Inst. Pasteur, 1907, xxi, 525.

² Möllers u. Heinemann: Ueber die stomachale Anwendung von Tuberkulinpräparaten. Deutsch. med. Wchnschr., 1911, xxxvii, 1825.

³ Freymuth: Ueber Anwendung von Tuberkulinpräparaten per os. München. med. Wchnschr., 1905, lii, 62.

⁴ Huhs: Therapeutische Versuche mit stomachaler und inhalatorischer Darreichung von Alttuberkulin. Beitr. z. klin. d. Tuberk., 1907, vii, 1.

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5/100 mg. O. T. subcutaneously, took by mouth 1,000 mg. O. T., with no effect, even when the gastric juice was neutralized according to Freymuth. Laffert and Dieterlen could get no reaction in tuberculous guinea pigs by this route. Krause¹ obtained good results in the treatment of glands and fistulæ. Hager and Köhler also have had some therapeutic success.

In the oral route we are also deprived of the benefits of the local reaction as a guide. In view of the possibility of cumulative action, of the fact that in many cases the tuberculin is not absorbed at all, and of the possibility of its acting unfavorably on tuberculous lesions of the alimentary tract, the oral route is objectionable. It was advocated by Krause because the patient can take a supply of capsules home with him. But supervision of a tuberculin patient is essential to success. Tuberculin (B. E.) in capsules for oral use is marketed as Phtysoremid.

Kapralik and v. Schroetter² administered tuberculin by inhalation or insufflation. They used a spray, as suggested by Moeller. Very much tuberculin is wasted by this method. The dosage is extremely inexact and the danger great.

The Intrabronchial Route.—Jacob³ gave what he called a lung infusion, in 1904. It is really an intratracheal or intrabronchial injection. The tuberculin is rapidly carried away by the lymph paths, and probably never reaches the focus. Liviérato gives the tuberculin directly into the lung.

¹ Krause: Ueber innerliche Anwendung von Kochs Bazillenemulsion (Phtysoremid). Ztschr. f. Tuberk., 1907, x, 508.

Löwenstein: Die innerliche Darreichung des Alttuberkulins. Ztschr. f. Tuberk., 1906, ix, 392.

² Kapralik u. v. Schroetter: Erfahrungen über die Wirkung der Einführung von Tuberkulin im Wege d. Respirations Apparates. Wien. klin. Wehnschr., 1904, xvii, 583, 617.

³ Jacob: Ueber die Bedeutung der Lungeninfusionen für die Diagnose und Therapie der Lungentuberkulose. Deutsch. med. Wehnschr., 1904, xxx, 945, 1024.

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The Rectal Route.—Rectally, tuberculin has been given in suppository and by enema. It seems entirely inert, thus.

The Cutaneous Route.—The cutaneous route has been advised by Pöppelmann¹ in advanced cases and by Wallerstein.² The argument is that such patients tolerate only small doses. We do not see any advantage, however, in giving the dose cutaneously, since by this method we are not sure of how much is absorbed at any one time. By the subcutaneous route the exact dose required can be administered with the certainty that it will be absorbed. The intracutaneous route is too sensitive for use. The local reactions occurring even with small doses are intense and painful.

The percutaneous route has been used by C. Spengler. It is known also as the dermic method. The tuberculin is rubbed into the skin to the amount of 1, 5, 10 mg.

The Intravenous Route.—The intravenous method was first used by Koch. He thought he obtained higher agglutination values by this method. But Bandelier and Roepke³ obtained equally high values by the subcutaneous route. Denys, too, has used it. Rothschild⁴ and Heermann⁵ have reported favorable results. The advocates of this route argue that the tuberculin easily reached the focus of disease, whereas in the subcutaneous method it is bound, to some extent, by the local cells. This method, too, lacks the assistance of the local reaction. Whether it is of any ad-

¹ Pöppelmann: Behandlung der Tuberkulose mittels Haut-impfung mit Tuberkulin. Berl. klin. Wehnschr., 1910, xlvii, 1930.

² Wallerstein: Ueber den diagnostischen Wert der v. Pirquetschen Reaktion und die Behandlung der Tuberkulose mit Tuberkulin-Cutanimpfungen. Berl. klin. Wehnschr., 1911, xlviii, 426.

³ Bandelier: Ueber die Heilwirkung des Neutuberkulins (Bacillenemulsion). Ztschr. f. Hyg. u. Infektionskrankh., 1903, xliii, 315.

⁴ Rothschild: Report of twenty-five cases of tuberculosis treated with intravenous injections of tuberculin. California State Jour. Med., 1906, iv, 231.

⁵ Heermann: Ueber einen schmerzlosen Injectionsmodus der Alttuberkulins. Ztschr. f. Tuberk., 1905, vii, 60.

vantage to the patient to have the entire dose of tuberculin suddenly introduced into the circulation there are not enough data to say. But that the consequences might be alarming should the dose be too large is much to be feared. Reactions may occur within an hour. Griffiths¹ reports a reaction to 105° F. when a dose was given intravenously by mistake (in the arm), although the patient had had no previous trouble from his doses. There was no local reaction. This case illustrates well the danger, although the patient made an excellent recovery from the reaction.

The Intrafocal Route.—The use of tuberculin intrafocally, that is, a method by which the tuberculin is brought into immediate contact with the diseased area, was instituted at an early date. Senger, Crocker and Pernet advise intrafocal use in lupus. We do not know of its use in pulmonary tuberculosis, but it has been injected into tuberculous joints (Béraneck, Rosenbach). Others have applied tuberculin directly to broken-down glands and to sinuses. The local reactions seem beneficial, but care must be used to prevent the absorption of quantities large enough to give severe systemic disturbance.

On the whole, it cannot be said that the subcutaneous route has at all been displaced by any of the others proposed. In accuracy of dosage and in multiplicity of safeguards it ranks deservedly highest. H. W. Crowe,² stimulated by Moro's statements as to the effect of the central nervous system on the tuberculin reaction, adds 4-per-cent. eucain lactate to tuberculin before injecting it subcutaneously. He hopes to make deductions of therapeutic interest from this work.

¹ Griffiths: Studies in pulmonary tuberculosis, its dissemination, specific diagnosis and treatment, and some points in its pathology. Sydney, N. S. W., 1911.

² Crowe: An experimental investigation into the question of the possibility of modifying the effect of an inoculation of tuberculin by combining with it a local anesthetic. *Lancet* (London), 1911, i, 366.

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In deciding what patients with pulmonary tuberculosis are fit for treatment with tuberculin we must keep in mind that tuberculin is not an antitoxin. It does not directly neutralize or inhibit any poison. Nor is it a bactericide, in the sense that it directly and immediately exerts a pernicious influence upon the infecting agent, the tubercle bacillus. In the previous pages it has been fully explained that tuberculin acts by stimulating the natural resources of the body. By the inflammatory changes it induces at the focus of the disease it promotes the contact of the virus with the defensive fluids and cells of the body. But how much protection this contact will afford depends, of course, upon the defensive power of the serum and cells. Likewise the output of antibodies provoked by the tuberculin is dependent in quantity or kind upon the condition of the body as a whole; and we arrive, therefore, at the inevitable conclusion that tuberculin can be of no help if the resources of the body are already exhausted. Cachectic patients, with the nutrition badly impaired, have, for this reason, little to hope from a tuberculin therapy. Especially is this the case if the ordinary hygienic-dietetic measures have had no good influence upon the nutrition, or the activity of the lesion.

The converse of the proposition just expounded is that every case of pulmonary tuberculosis is fit for tuberculin therapy, unless the nutrition has been so impaired that the patient is palpably incapable of stimulation. When the patient is not definitely cachectic it is, of course, well to give him the benefit of the doubt, although not much can be expected in such borderline cases.

Patients Suitable for Treatment.—Although the two propositions stated above are a sufficient guide for any judicious physician in selecting cases for tuberculin therapy, we will review in somewhat greater detail the kinds of

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patients to whom tuberculin may be given with chance for success.

1. Febrile cases. Mild fever is not in itself a contraindication, if the nutrition is good. Rest in bed should be the first antipyretic measure attempted. If the fever persists tuberculin may be tried cautiously. When the temperature is not over 100° , and has persisted in spite of rest, it is permissible even to have such a patient come to a clinic for his tuberculin. In such cases, if the exertion of the trip causes more than a very slight rise in temperature, the trips should be discontinued, and the tuberculin given at the patient's home. Although in some cases the tuberculin acts as an antipyretic, yet the prognosis is, of course, not good in persistently febrile patients.

2. Tachycardia. A rapid pulse, even without fever, demands rest in bed and appropriate treatment. If the tachycardia persists tuberculin is not contraindicated, although the prognosis is much depressed by such a condition. The rule for admitting such a patient to an ambulant tuberculin clinic is the same as that for mildly febrile cases.

3. Advanced and moderately advanced cases. If the patient is afebrile, the pulse not very rapid, the nutrition not cachectic, then the large extent of lesion does not render him unfit for tuberculin treatment. Indeed, it may be given as a general rule that it is not so much the extent as the activity of a lesion which makes treatment difficult. Probably the most striking results of tuberculin are obtained in advanced or moderately advanced patients when the nutrition has suffered (but not hopelessly), and when the mild fever is controlled by rest. In such cases the stimulating effect of tuberculin is rapidly evident; the patient becomes capable of moderate activity, and is much less likely to suffer from relapses.

4. Early cases. Such patients, although they apparently do well under any treatment, form proper subjects

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for tuberculin treatment; since such treatment tends to protect them from relapse, and insures, to a greater degree, their continued ability to work.

5. Latent tuberculosis. Children of infected families, who show no physical signs of pulmonary tuberculosis, but who are evidently below par physically and show tuberculin hypersensitiveness, are fit subjects for tuberculin treatment. This is sometimes known as the prophylactic treatment of the pretuberculous child, but it is more correctly the curative treatment of a mild, concealed tuberculosis.

Contraindications.—Under choice of patients we discuss those cases of pulmonary tuberculosis who, *per se*, are fit or unfit for tuberculin therapy. By a contraindication we mean a condition which renders tuberculin treatment undesirable in a pulmonary case *per se* quite fit for treatment.

A contraindication to tuberculin treatment can exist only when there is a complicating disease, upon which tuberculin would have a deleterious influence, at least to such an extent that the damage here done would outweigh the good that might be expected. We may say at once that we know of no organ that can be harmed by therapeutic doses of tuberculin. Many writers cite long lists of contraindicating diseases, such as bad nephritis, broken cardiac compensation, epilepsy, etc. The truth of the matter is that such conditions are not contraindications, but unfortunate complications that hinder any treatment. If the patient is suffering seriously from cardiac or nephritic disease, for example, there is, of course, little to hope from tuberculin, but this is not because tuberculin would here do any harm to the heart or kidney, but because the kidney or heart condition prevents the system from responding to treatment. Tuberculin may, then, be given to any patient whose complications have not too much depressed his resisting power. The coexistence of lues and tubercu-

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losis is of especial interest. The lues should, of course, be treated specifically. As we do not know of any evidence for the harmful effect of tuberculin upon the course of lues, we see no reason for not using tuberculin upon a luetic phthisic, if the tuberculin is not otherwise contraindicated. There is no objection to using tuberculin in pregnant women; on the contrary, much good can be accomplished here for mother and child.

Some of the lists of contraindications have, for their justification, the claim that a tuberculin reaction would be dangerous. It is conceivable, of course, that a badly injured cardiac or renal system might have its balance entirely overthrown by a severe tuberculin reaction. However, if a patient so nearly *in extremis* were given tuberculin at all (and we do not see why he should) it should certainly be given so cautiously that more than a mild reaction would be out of the question.

The fact that the ophthalmic test has been given is no contraindication to treatment by tuberculin, if the reaction has subsided, since a flare-up rarely occurs except after large diagnostic doses. In all our experience we have seen only two instances of a flare-up after therapeutic doses. Phipps, No. 5,245, A. C., female, age 48, white, had a + + reaction to the 5-per-cent. O. T. in the right eye on February 16, 1912. On February 20th she was given B. F. 0.000,000,01 c. c. On March 15th she had reached 0.000,000,5 c. c. After this dose she had slight local pain and a flare-up of the right eye, lasting a few days. Phipps, No. 8,271, M. B., age 21, colored, had a + + reaction to the 5-per-cent. O. T. in the right eye on February 6, 1912. On February 16th she received B. F. 0.000,000,1 c. c. On March 5th she had reached 0.000.000,5. After this dose her temperature rose to 100°, and the right eye reaction flared up.

In both these cases the flare-up subsided in a few days,

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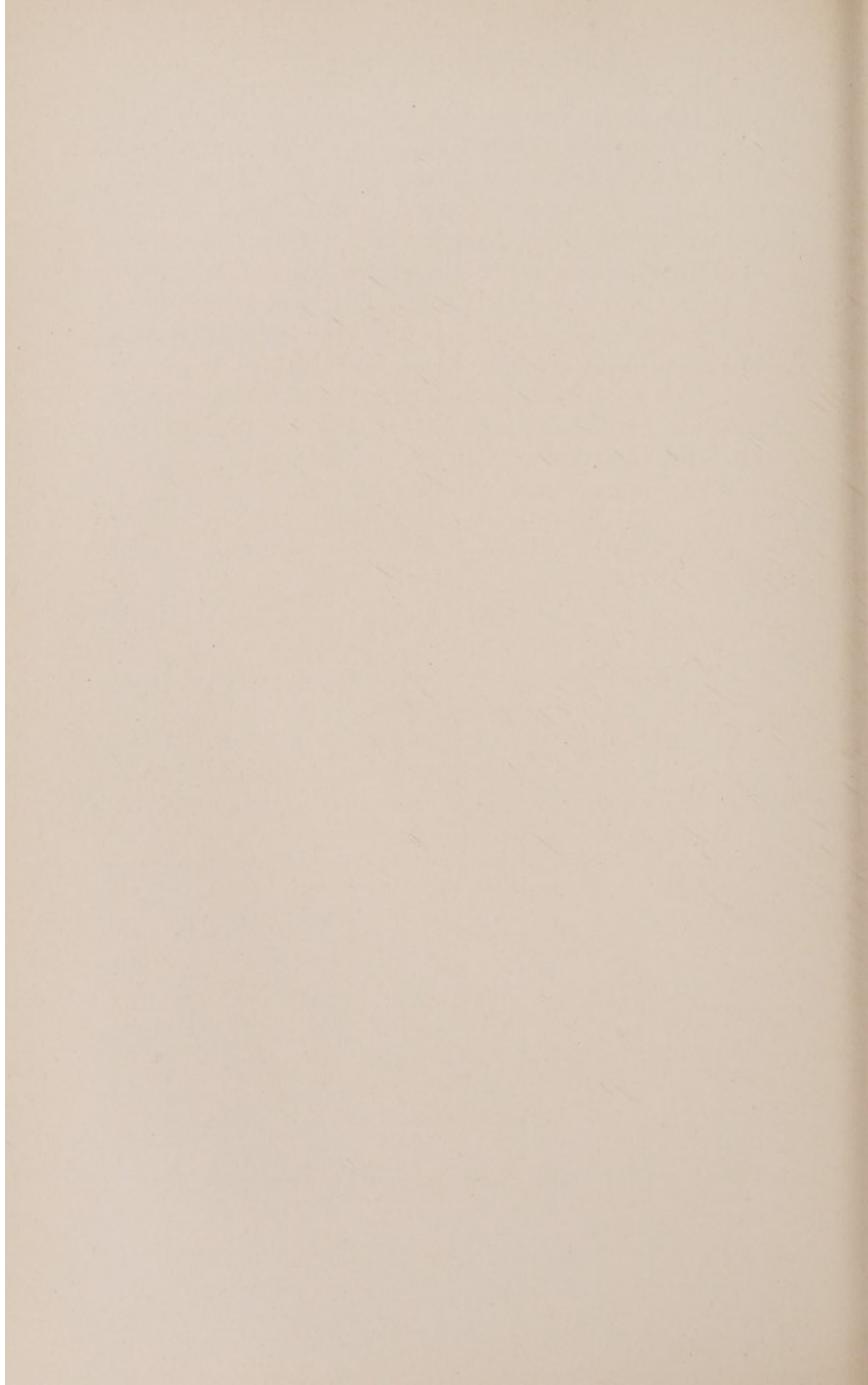
and the tuberculin treatment was continued without further trouble.

The question may arise as to what patients are best fitted for tuberculin treatment in an ambulant clinic. Assuming that tuberculin is a favorable factor, is it so helpful that a patient with pulmonary tuberculosis shall be advised not to enter a sanatorium, but to take tuberculin at his home or at a dispensary? The question has been discussed with vigor in England and Germany, and sometimes the extreme attitude has been taken that tuberculin makes sanatoria, to a great extent, useless. Such an attitude is unjustifiable. Tuberculin must, at present, be regarded as a subsidiary agent, and, as such, should be combined with the best therapeutic measures available. Rest, hygiene and fresh air ought to accompany tuberculin treatment, just as much as tuberculin ought to accompany them, whenever possible. The benefit of the sanatorium treatment should not be denied to patients, especially to the poorer ones, merely because a tuberculin dispensary is at hand. The function of the latter is supplementary to that of the sanatorium. Patients who have been at the sanatorium and have returned to work, whether or not they have already had tuberculin, if they fit the requirements already described, are proper subjects for an ambulant clinic. For such, night or Sunday classes may eventually be instituted. Another group would comprise those who cannot be persuaded to enter a sanatorium, or for whom, at least for many months, no place can be found.

That tuberculin can be given satisfactorily at an ambulant clinic has been shown. Supervision can be had by visiting nurses and by individual conferences with the physician. It is true that more care should be used in arranging doses in the cases of patients who are ambulant, or even at work, than for those resting in a sanatorium. But the difficulties are not at all great. It is true

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also that tuberculin can be given to sicker patients in a sanatorium than it is possible to do in a dispensary, since in the latter case the trips to and from the clinic would counterbalance the possible good accomplished by the tuberculin. Nor would tuberculin, as an antipyretic, have much use in an ambulant clinic, unless the patient's temperature does not rise to 100° F., since rest in bed is so essential to the treatment of fever. In fact, the treatment of a mildly progressive case in an ambulant clinic should be undertaken only when prolonged rest in bed has had no visible effect, and when no measures can be devised for administering the tuberculin to the patient in bed.



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