TUBERCULIN TREATMENT IN PULMONARY TUBERCULOSIS*

By WM. LITTERER, A.M., M.D.,

Professor Bacteriology and Pathology, Vanderbilt Medical College.
Nashville, Tenn.

Soon after the announcement by Robt. Koch in 1882 of the discovery of the tubercle bacillus there quickly followed many attempts to destroy the bacillus in the tissues of the infected organism by the administration of various substances found to kill it in vitro. All such attempts were, of course, futile, especially since many of the substances that were recommended which if used in sufficient strength would have killed the host as quickly as the parasite. The literature during that period abounded in wonderful cures and marvelous results obtained by some, from the use of these so-called "false specifics," only to be followed by others, by deep disappointment and ultimate abandonment of the remedies. Today, a sign of the times is the paucity of publications referring to fresh or new remedies aside from the specific treatment of tuberculosis by the various tuberculins. A perusal of current literature reveals an unmistakable increase in the actual practice of the specific treatment of tuberculosis and also palpable progress in the growth of our knowledge of the main lines along which it should be conducted.

When Koch in 1890, proclaimed his sensational discovery of a specific remedy against tuberculosis, perhaps there never was an announcement made in the realm of medical science that carried with it so much hope as did that of the discovery of tuberculin. Koch made two claims for tuberculin: first, that it causes a specific reaction in tuberculous individuals; and, second, that it has curative properties. For its administration he laid down the following very sensible rules, and if they had been followed the world would have been spared those dreadful scenes which resulted from its early trial: 1. Only patients that have little or no fever and in whom the process has not advanced too far, are suitable

for treatment. 2. One begins with a very small dose and increases it so slowly that only very slight reactions or even none at all take place. 3. If reactions take place tuberculin must not be injected again until the temperature has been normal for one or several days. 4. The treatment with tuberculin must be repeated till, after an interval of three or four months, the capability of reaction is permanently extinct (Pottenger, p. 168). These rules, although formulated eighteen years ago, are even safe for today. Of course all these years of experience have taught us different methods of administration as well as its employment in selected advanced cases. Koch's rules were absolutely disregarded. Large doses of tuberculin were administered to all sorts of cases, and many a poor, far-advanced consumptive was hurried to his grave. A patient for instance was given tuberculin and reacted to 104 deg. F. on the following day, when he received a second dose with similar results. This was continued in many cases until death ensued. It was not long before the majority of physicians dropped the new remedy with as much avdity as they had taken it up. The age of "tuberculin terror" may be said to have begun at this time and he who used tuberculin was looked on by many as a criminal. In spite of the general disappointment which followed its misuse, in spite of the fact that much harm was done and death hastened in many instances, there were a few great and far-seeing minds who grasped the meaning of the remedy and realized that Koch had introduced a therapeutic agent which was destined to live. To a few German physicians, Goetsch, Spengler, Krause, Heron, etc., led by Koch, and to Trudeau, Von Ruck, Pottenger and others in this country have been instrumental in causing a reconsideration and new trial of this remedy.

*Read before the Upper Cumberland Medical Society at Cookeville, Tenn., May 24 and 25, 1910.

Notwithstanding their consummate efforts in behalf of tuberculin this revulsion of feeling on the part of the profession lasted for some years, but about 1898 interest in the remedy was revived. Infinitesimal doses were given, and an attempt was made to render reactions of minimal occurrence instead of considering them the great desideratum. The present period could appropriately be called the "tuberculin renaissance era," which began a few years ago. Apathy has given way to enthusiasm. Again the scientific world is inflamed and the pendulum is swinging the other way. It is well for us to pause a bit lest this very enthusiasm lead us to discredit a method which, when used rationally and understandingly, is unquestionably a most valuable aid in the treatment of tuberculosis.

THE TUBERCULINS.

The term "tuberculin" is a broad one and has been applied to nearly all products made from the tubercle bacillus, but in reality belongs only to those which are made from the culture fluid on which bacilli have been grown. For the past six years I have been making my own tuberculins (according to the formulas given below), not only for therapeutic uses but for experimental purposes. In conducting the various experiments incident to the immunization of the lower animals, it is manifestly apparent that absolutely fresh products be obtained from bacilli of known virulence. These bacilli represent three separate and distinct types, viz.: Human, bovine and avian bacilli. For therapeutic purposes I have been in the habit of using one of five different types or strains of human bacilli which were isolated from various tuberculous subjects for the purpose of exchanging one strain for another in case the patient failed to respond to the treatment as rapidly as he should. I have deemed it wise and expedient in a number of instances to mix equally the five human strains or to use solely the tuberculin made from the bovine or avian bacillus. By such a procedure I have observed that after a change of this sort that patients

(where they appeared not to be doing well) were again on the road to health even after the measures previously applied seemed to have reached the limit of their efficacy.

There are described between fifty and sixty varieties of tuberculin. Of these only a few will be considered while others being either modifications of these or having proved inefficacious.

The first used was Koch's original tuberculin, "O. T.," called also "Old" Tuberculin, to distinguish it from his more recent products, "New" Tuberculin. (1) The original tuberculin Koch (O. T.) is the concentrated germ free culture media (Glycerin bouillon), in which the tubercle bacilli were allowed to grow for several weeks. (2) Bouillon Filtrate "B. F." is the unheated, unconcentrated, filtered (through porcelain) bouillon culture of human tubercle bacilli. (3) "New Tuberculin," Tuberculin R., "T. R.," or "Tuberculin Residue." This is prepared by growing a virulent culture of tubercle bacilli. They are dried in the dark in vacuo and then pulverized. The powder thus obtained is suspended in distilled water and centrifugated at very high speed for about thirty minutes. The water (which is called tuberculin obere "T. O.") is then drawn off, discarded, and the bacterial residue is again dried in vacuo, as above, and treated in the same manner. This is done for several times. It is supplied in liquid form, containing 2 mg. of the powder to the C.C. of 20 per cent. glycerin solution. (4) Bacillen Emulsion, "B. E." This is Koch's latest product, which he has suggested for active immunization. It consists of an emulsion of the ground-up tubercle bacilli in equal parts of glycerine and normal saline solution. (5) Bovine Tuberculin. Perlsucht Tuberculin (P. T. O., Spengler) is made from the bovine bacilli without subjecting the culture fluid to heat which is believed injures its activity. The bacilli are grown until they form a covering on the culture medium when they are removed by filtration and the filtrate concentrated by placing

it in an incubator until it equals one-half of its original volume. It is then restored to its original volume by the addition of glycerin.

Spengler and Pottenger find that preparations made from the bovine bacillus are much less toxic for human infections than those of the human bacillus and at the same time they find them more active in their stimulation of the machinery of immunization as is shown by their power to increase the specific agglutinins of the blood. There are many other preparations that are more or less well known, viz.: Antiphthsin (Klebs), the water extract of tubercle bacilli (Von Ruck), Hunter's modification of old tuberculin, Beranek's tuberculin, Von Behrings tulase and many others.

CHOICE OF TUBERCULIN.

Of the three forms of tuberculin mostly in use today are the Koch's New Tuberculin T. R., B. E. and the (B. F.) of Deny's, with bovine tuberculin rapidly gaining popularity. It would seem, theoretically that the B. E. would be able to produce the greatest amount of anti-bacterial immunity, while Deny's tuberculin "B. F." appears to be best suited for the production of an anti-toxic immunity. This tuberculin contains the products of the tubercle bacilli disintegrating during the growth of the culture, as well as the unchanged products of the tubercle bacillus given off in its growth. It is less toxic than the Koch's Old Tuberculin "O. T." and undoubtedly possesses immunizing properties which are destroyed in the "O. T.," as a result of the prolonged heating to which it is subjected. The Bacillen Emulsion does not represent the products of bacterial action such as are found in the "O. T." and "B. F." and therefore to my mind is one of the reasons why it should not be solely used in the treatment of tuberculosis. Again it is slow in its absorption and will cause many more general and local reactions as compared to the Bouillon filtrate "B. F." Up to two years ago I have used only the "B. E.," since that time equal parts of the "B. F." and "B. E." have been employed with ap-

parently very much better results than with the "B. E." alone. I am strongly of the opinion that the ideal therapeutic agent for the treatment of tuberculosis is the combination of two products, viz.: Equal parts of the Bacillen Emulsion "B. E." and Deny's tuberculin "B. F." This mixture would combine whatever immunizing properties that exist in either the tubercle bacillus or the culture fluid.

ACTION OF TUBERCULIN.

Whenever a cure of tuberculosis takes place it consists in establishing upon the part of the infected individual an immunity to the tubercle bacillus and its toxins. All bacterial diseases depend for their recovery upon the favorable action of the machinery of immunization. A cure from diseases of bacterial origin may be considered synonymous with immunity. This immunity may be ever so transitory as is noted after pneumonia or somewhat more lasting as is observed following diphtheria, or it may be quite permanent as we find it after syphilis, smallpox, etc. When the body tissues are invaded by specific micro-organisms a struggle for mastery at once ensues. The anti-bodies which are normally found in the tissues destroy some of the invading bacteria, liberating endotoxins, etc., which in turn stimulate the body cells to the formation of more anti-bodies. In other words, any toxin which, when introduced into the organism, has the power of stimulating the system to the production of anti-bodies which are for that particular poison. The ultimate outcome of the battle between the bacteria and body cells of the individual depends upon the number or virulence of the bacteria on the one hand and upon the capability of the body cells to respond to the stimulation on the other. The anti-bodies found in an animal as a result of the recovery of an infectious disease are of several different toxins, preceptins, stimulins and coagulins, have thus far been studied and there may be still others as yet undiscovered.

It is manifestly important to know that these specific anti-bodies above noted can be

produced in many diseases by the inoculation of bacteria which have been killed at their minimum thermal death point. The anti-bodies that are formed as a result of injecting a certain type of bacteria are specific for that particular micro-organism. Thus typhoid bacilli cause typhoid anti-bodies; Staphylococci produce Staphylococci anti bodies and tubercle bacilli ("Bacillen Emulsion and products) manufacture anti-bodies for the tubercle bacillus. So the use of tuberculin is based on the principles of artificial protection, and it is our desire to obtain an over-production of anti-bodies in order to build a defensive armament against which the tubercle bacillus and its ravages will be impotent.

In tuberculin therapy we propose to produce an active immunization. To establish such an immunity it is absolutely imperative that the toxins (tuberculins) act with regularly progressive intensity on those groups of cells which produce toxin immunity. Stimulations of a slight or stationary nature are not sufficient to set in motion the machinery of immunization. It has been shown by Roux and Von Behring that properly spaced many small increasing stimulations are of greater import than one large stimulation. Likewise Trudeau affirms that infinitesimal doses of tuberculin, methodically increased, which produce only slight stimulation of the defensive resources of the organism, result in a well-marked toxin immunity, as shown by increased toleration to large doses of toxin, while large doses or too rapid an increase may bring about anaphylaxis or hypersusceptibility and an aggravation of all the symptoms of the disease. By the inability to control the liberation of toxins (tuberculin) manufactured in the body of a tuberculous subject, accounts for the failure in many cases to effect a complete cure. If the tuberculous foci are liberating large doses of the toxins at irregular intervals over an extended period nothing but disaster could ultimately result to that individual. Ringer states that "While the bacilli are mainly responsible for the local conditions in the lungs,

the toxins are the cause of the emaciation, the loss of strength, the febrile temperature, the rapid heart action, the night sweats; in short, the constitutional manifestations. The origin of this toxemia of tuberculosis can be accounted for only by the assumption that the toxins and soluble proteids manufactured at the site of bacillary invasion are taken into the blood and lymph streams and carried to all parts of the body."

CLINICAL RESULTS.

The final test of all remedies must be clinical results. Theoretically there are many remedial measures that are lauded to the skies but when they come to the practical application prove dismal failures. This is not so with tuberculin. It has withstood the test of time. Enormous amounts of literature coming from masters in this country, in England and on the continent are lending willing testimony to its inestimable value. Many comparative tables are daily noticed in the various journals showing the benefit derived as a result of tuberculin administration as compared with the untreated patients subjected to identical environments, etc. In the Johns Hopkins Tuberculosis Dispensary, conducted by Hammand and Wolman, in which they recently report that they have had fifty-seven cases of pulmonary tuberculosis on tuberculin treatment (T. R. and B. F.) for at least ninety days with the following results: Ten patients were apparently cured, in sixteen the disease arrested, twelve were improved, in eighteen the disease was progressive and one died. In selecting the cases the stage or the extent of the disease is not considered. In the out patient department of the Massachusetts General Hospital, Boston Consumptives' Hospital and the Good Samaritan Day Camp, tuberculin treatment was given the dispensary patients under the supervision of Drs. Hawes and Floyd. They report that out of 143 tuberculous patients treated with tuberculin (B. E. & B. F.) during the past four years, nineteen have died, sixteen have shown no improvement, while 108 have been benefited to

a greater or less degree. They claim that in no instance have they been able to see that tuberculin has done the slightest harm; reactions have been rare and invariably of a very mild type. In incipient pulmonary tuberculosis they regard tuberculin as a factor in increasing body resistance and in maintaining this resistance so as to prevent relapses. In more advanced pulmonary disease tuberculin will often alleviate distressing symptoms, prolong life and occasionally help to arrest the process. In localized or "surgical" tuberculosis, tuberculin has a marked beneficial effect. They conclude by saying that Dispensary patients can be treated with tuberculin not only with perfect safety, but with distinct benefit, providing that there is a close personal co-operation between patient and physician. Of course it goes without saying that the outdoor hygienic dietetic, etc., regime was rigidly adhered to. An interesting article by Lawra Brown emphasizing early treatment of tuberculosis, appears in the *New York Medical Journal*, Nov. 20, 1909. He has compiled the ultimate results obtained at the Adirondack Cottage Sanitarium, covering twenty-two years. He finds that the records show that 52 per cent of the patients in an incipient stage, 25 per cent of the moderately advanced, and less than 2 per cent of those in the far-advanced stages are alive. In other words a patient in the incipient stage has at least twenty-six times as good a chance of permanent recovery as one in the far-advanced stage. He says that not every patient with tuberculosis will recover, no matter how early his case is diagnosed, and no matter how soon put under the most approved treatment. But in an early case a patient has twenty-six times better chances for permanent recovery than in a late one.

PERMANENCY OF RESULTS.

The question of paramount importance to all patients after they have been apparently cured is whether or not they will remain cured. It is manifestly apparent that the results obtained in tuberculin treated cases are

more permanent than in those treated without it. Patients who get well without treatment or with the usual open-air-hygienic dietetic treatment, are more apt to have a quiescence rather than a cure. This is shown by the fact that many of them will still react to tuberculin, which they would not do if they were cured, and also by the fact that a greater percentage of those suffer relapses than of the tuberculin treated cases. (Pottenger p. 203.) Trudeau, who has used tuberculin over a longer period of time in more cases and more conservatively than any other man in these United States, discusses the post-discharge mortality between patients treated and those that were untreated with tuberculin at the Saranac Lake Sanatorium. He says that 18 per cent more of the treated incipient cases are living than those of the untreated, while 25 per cent more of the advanced cases who received tuberculin are living than those who did not. In effecting a cure the struggle for mastery is essentially a local one. Lymphocytes are prominent in the formation of the tubercle, and the wandering leukocytes participate together with connective tissue cells in localizing the bacilli. If the organism is successful in effectually localizing the tubercle bacilli, a more or less rapid process of disin-tegration or bacteriolysis ensues which destroys the bacillus and disposes of its products. On the other hand in the so-called arrested cases where complete recovery has not taken place we find that in the center of the tubercle that a great many cells have died in consequence of the direct and prolonged exposure to the toxin, and caseation of greater or less degree is the common result. This caseated material really protects the enclosed bacilli from further lytic action by the living cells. Owing to the restricted action of the pent up tuberculin toxin, the body cells not composing the tubercle fail to get the proper stimulus to resist its action when the constitutional condition is in a favorable state for this. This fact forms the chief rationale for specific therapy in tuberculosis by tuberculins, for it

is desirable to impress the whole organism with the specific stimulus in sufficient quantities and at proper intervals to maintain a high resistance (E. R. Baldwin). If tuberculin were not used in these arrested cases you will be apt to find the fire still smouldering, sooner or later to break out into a serious conflagration. The pent up toxins in the tubercles are now at the mercy of the non-immunized body cells. Any immunity now that results often comes too late to be efficacious in saving life. By the employment of properly spaced doses of tuberculin in these cases there results a local stimulation of the tuberculosis foci (tubercles) which shows itself as a hyperemia thereby causing more blood to be sent to the part and consequently new protective substances are brought to bear upon the bacilli in the foci of infection. The area of infection previously lacking in vascularity is not only flooded with a greater amount of blood, but with a blood whose immunizing properties have been greatly increased. Again tuberculin does another thing, and that is it produces a more rapid formation of fibrous tissue around the foci of infection. The irritation caused by the local reaction on the tubercle is responsible for this fibrous tissue change. From this we can readily understand that the addition of tuberculin treatment must not only increase the chances of cure but must enable this result to be produced in a shorter time.

RESULTS DUE SOLELY TO TUBERCULIN.

The most convincing results as to the efficacy of the use of tuberculin comes from Bonney of Colorado.

He selected forty-two cases of chronic pulmonary tuberculosis without symptoms referable to mixed infection. It was recognized that all patients should represent, if possible, the same general type and stage of the disease, and conform more or less closely to a fixed regime. It seemed highly desirable that there should be eliminated all sources of confusion arising from climatic influence or change of environment. To this end patients included in this group were selected with ex-

treme care. In view of the uncertainties attending its employment, no individual was permitted to undergo the treatment, whose general condition or previous progress had been entirely satisfactory, or who exhibited appreciable temperature elevation. On the other hand, an effort was made in the selection of cases to include only those who, in spite of a continued residence in Colorado, under appropriate conditions of daily life, had failed to secure an entire arrest of the tuberculous process. It was believed that more definite information concerning the effect of the treatment could be secured by limiting its application: to those whose condition had been almost stationary for prolonged periods. Of all the cases comprising this group, the average period of residence in Colorado, with practically unchanged environment, was two years and eleven months, the longest being ten and one-half years, the shortest six months. A remaining active of the tuberculous process was present in all cases, as evidenced by physical signs: cough, expectoration and bacilli. A new method of treatment was hailed with enthusiasm by these patients as precursory of possible future recovery, this introducing a psychic element impossible of elimination. In summing up he says that in no instance has he been able to detect permanent injury from the treatment. On the other hand, conspicuous improvements have been noticed in some cases. In the majority of the cases demonstrable progress has been established, but it is probable that in some cases the psychic element has been a factor of considerable importance.

A number of cases showed a material diminution of cough, and sometimes its complete cessation. The sputum has been markedly lessened, in many cases. In a few instances a conspicuous diminution of bacilli has been noted several months after the inauguration of this treatment. A gain in weight has been exhibited by several patients whose previous efforts in this direction had proved unavailing. In no case has there been a loss of nutri-

tion. Of the forty-two cases, he reports in detail ten cases showing marked improvement. Of the remaining thirty-two in this group, fifteen may be said to have exhibited some favorable effect from the administration of the remedy. In twelve there was no appreciable influence properly attributable to the tuberculin. Five exhibited an increase of cough and expectoration after each injection to such an extent that the tuberculin was suspended after three or four doses.

RESULTS.

Within the past six years I have been able to collect fifteen selected pulmonary cases in which thorough tests were given to fresh air, good food, carefully regulated living, rest, hydrotherapy, etc. With this treatment alone a distinct improvement was noted in all of the cases several months after its inauguration. Several continued to improve one year afterwards while others seemed to have reached their road's end in from three to six months in spite of everything that could be done in the modern way of treating tuberculosis with the exception of the employment of tuberculin.

The cases were favorable ones for the specific treatment. Many exhibited little or no fever. All had physical signs, cough, expectoration and bacilli.

Tuberculin was given with the following results:

Four cases cured or arrested.

Two cases improved as shown by gain in weight, lessened cough and expectoration and loss of bacilli. Physical signs are still apparent but much improved.

Four cases improved, as evidenced by increase in weight, diminished cough, and expectoration, with a marked diminution in the number of bacilli.

Five cases unimproved.

Out of this number I have at present six that I am administering the tuberculin with slow but progressive improvement. In a later communication I intend to discuss the entire fifteen cases in detail.

SHOULD TUBERCULIN BE USED ON A PATIENT WITH FEVER.

Pottenger is authority for the statement that a slight rise of temperature, due to the tuberculous process which does not exceed 101 degrees is best combatted by a combination of the open-air, dietetic, hygienic and tuberculin treatment. He says that it is not an uncommon experience to find a rise in temperature of this kind which has persisted for some time, yield in a short period to injections of minute doses of tuberculin.

Krause has recently obtained excellent results from the administration of tuberculin to febrile patients. He reports a permanent disappearance of the fever in all cases, and suggests at least a tentative administration of the remedy among a few patients who have resisted all other measures.

Bonney of Denver has quite recently had occasion to employ the tuberculin in six cases exhibiting persisting fever of from 102 degrees to 103 degrees F. daily despite prolonged rest in bed in the open air. In three cases no appreciable effects were noted; in one the temperature receded within a few days to normal and has remained so for four weeks; in two cases the temperature has gradually receded to the neighborhood of 99 degrees and 99.5 degrees F. That such injections act beneficially I have been able to prove to my satisfaction for the past few years. Repeatedly have I seen such temperature yield to this treatment when they had refused to yield until the tuberculin was given.

Theoretically the above contention seems unreasonable, for it is generally believed that the fever is due to the system's being surcharged with toxins from the tubercle bacillus; and, it would seem that to inject more toxins, would be only adding fuel to the fire. Professor Wright offers us an explanation of this action. He says that not infrequently the machinery of immunization fails to work to its full capacity in spite of the fact that toxins from the invading bacteria are being poured out into the blood stream. At such times vac-

cines injected into the tissue may stimulate the formation of protective bodies where those circulating in the blood have failed.

CONCLUSIONS.

(1) The efficiency of tuberculin as a therapeutic agent has been proved to such a degree that it has passed beyond the pale of controversy.

(2) Its administration should always be combined with rest, hygienic, outdoor treatment and in the vast majority of instances should be subservient to this.

(3) I am of the opinion that equal parts of the "Bacillen Emulsion" and "Bouillon Fil-

trate" represent at the present time the ideal therapeutic agent for the treatment of tuberculosis; for the reason that the mixture would combine whatever immunizing properties that exist in either the tubercle bacillus or the culture fluid.

(4) Statistics show that more than twenty per cent more permanent cures have resulted when tuberculin has been employed than where it has been omitted. (Trudeau & Pottenger.)

(5) Many patients running a slow but steadily down hill course, in spite of hygienic, dietetic and open-air treatment, improve under tuberculin.

I'anderbilt Medical College.

TUBERCULOSIS*

By JAMES JOSEPH KING, A.B., M.D.

Freeland, Pa.

Tuberculosis, scientifically speaking, is implantation and growth of the tubercle bacillus in the tissues of a human being or a lower animal. The tubercle bacillus is a rod shaped bacillus about one six-thousandth of an inch in length and about one hundred thousandth of an inch in thickness. The word tuberculosis is derived from the Latin word tuber, which means a root or a lump. It came to be applied to the disease now known by this name in this way. When post mortem examinations were made on people who had died of consumption, it was found that there were in those parts of the lungs which had not completely been destroyed, little lumps ranging in size from a mustard seed to a chestnut. Sometimes large numbers of these tubercles were found, at other times only a few were present. Some were soft and some were hard, and sometimes cavities were found and it was thought that this represented the various stages of the disease. Therefore, the lumps were called tubercles and the process which produced them was called tuberculosis.

It has been proven by historians that tuberculosis, as we know it, has existed for at least three thousand (3,000) years, and it is reasonable to assume that the disease existed long before it was recorded in history. Moses is credited by Biblical scholars with a knowledge of consumption, and they claim that he had reference to this disease in his figures of speech in Leviticus 24:13-16, and in Deuteronomy 28:20-22. Furthermore, it is claimed by some that one of the plagues inflicted upon the Egyptians was consumption. Hippocrates, in the fifth century before Christ, gave us such a good description of its ravages as to seem now to be only an exaggerated picture of what we see around us at the present day. Galen in the second century after Christ gave us a description of the disease as he saw it among the Romans, and from Galen's day to modern times the story of the disease is much the same.

It is beyond the comprehension of man to realize what tuberculosis means to the world. The disease exists in every part of the habita-

*An address delivered at the Mass Meeting at the Y. M. C. A., Freeland, Pa., on April 24, 1910.