Ernst (H.C.)

Koch's Treatment of Tuberculosis.

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KOCH'S TREATMENT OF TUBERCULOSIS.[1]

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GENTLEMEN:—By the kindness of the Medical Faculty, I have been requested to address you to-night upon a subject which is occupying the minds of all of your elder brethren in the medical profession at the present time, and to give you, as clearly as possible, some idea of what this seems to us to be, together with a few of the reasons for my personal belief in the efficacy of the new treatment against tuberculosis, as was apparently shown to me by the effects I saw while at Berlin.

What I have to say to you will be practically a repetition of an address I made Thursday evening in the amphitheatre of the Massachusetts General Hospital before the medical profession.[2]

I have had the honor of sharing in the introduction of this treatment in Boston; and the first patient

[1] Lecture delivered at the Harvard Medical School, Saturday, January 10, 1891.

[2] At the address to the members of the medical profession given by Dr. Ernst, at the invitation of the Staff of the Massachusetts General Hospital, in the operating theatre of that hospital, Dr. C. B. Porter made the following introductory remarks:

Gentlemen, Members of the Medical Profession:—"A member of the staff of this hospital, by laborious work in the laboratory of Professor Koch, of Berlin, by painstaking research in his own laboratory at the Harvard Medical School, has made himself an authority in bacteriology. Recently he has had exceptional opportunities, both by personal interviews with Professor Koch himself, and personal observation at the bedside in various Berlin clinics for acquiring a knowledge of the action of 'Paratoloid,' which is the name given to the fluid by Professor Koch, which he claims is of service in the treatment of tuberculosis. It seemed to the hospital staff eminently desirable that the profession should have an opportunity to hear from him the result of his experience, and it is by their invitation that you are here to-night, and that I have the pleasure of presenting to you, Dr. Harold C. Ernst."

upon whom it was tried in this city, is still under my care at the Massachusetts General Hospital in Dr. Tarbell's service and by reason of his courtesy. The number under treatment is for the present limited, because when we look at the matter soberly, we must all acknowledge that it is a great clinical experiment, and the impressiveness of the stage through which we are passing is one which will grow greater as time goes by. We, as medical practitioners, are doing a thing which has never before been known in the history of medicine. We are, at the suggestion of one man, employing a material of whose composition we are still ignorant. And we are doing this in perfect faith, and feeling we are justified in our course, because this material, and the suggestion of its employment, comes from one of the greatest medical minds the world has ever produced. This one fact of the general acceptance of Koch's paratoloid, and its employment against tuberculosis by the medical profession, says more than any one individual can find words to express, of the greatness of character of this man, who has been, to my mind, for a number of years, one of the most impressive characters that has ever crossed the medical stage. He is the one man in scientific medicine who thus far has never made a mistake. Going back some twenty years ago to the time of the Franco-Prussian war, through which he served as an assistant-surgeon, passing from that period to a struggle for a practice in an obscure north German town, without money, influence, or friends, he stands to-day at the pinnacle of the medical profession; and we all look to him for further developments in the line of his previous researches. He is practically the one man by whom the possibility of research in bacteriology has been laid open to us by the development of methods which enable the average man to carry out something

in the line of work in which he himself is engaged. This does not enter a claim for his absolute precedence in bacteriology, for there were others before him, Pasteur, of course, among them; but it is owing to the introduction of his methods that we have reached our present point.

This is one side of the question which should be impressed upon you. You are now passing through something similar to the experiences of forty-five years ago, when the first suggestion for the use of ether was made. I have been told of the excitement at that time by men who were then about your age, and it can only be compared to the excitement that is now going on in Berlin, and to a lesser extent in the other medical centres throughout the world. We are trying this material in the line of a great clinical experiment, to prove or disprove its efficacy.

The first thing to discuss before such an audience as you make up, is to indicate as clearly as I can, what this material is; and before I can definitely give you my idea of what it is, I must tell you what it is not. Probably what it is not, is the thing which has been impressed upon you that it is. In the first place this material is distinctly not a vaccine. It bears not the slightest resemblance to one, and it is very easy to see why, if you recall what a vaccine really is. A vaccine requires for its effect and action something in the nature of vitality — an organism. There must be something present capable of reproduction. It must have some vitality, and the best example is the "vaccine virus," which we see employed daily as a preventive against small-pox. A vaccine has distinctly the power of self-reproduction, if a minute amount is introduced into an abrased part, and a local reaction of a very marked degree is set up; this does not occur in our experiments with paratoloid, therefore this

material is distinctly not a vaccine. Again, it is distinctly not an attenuated virus. All the French methods, so far as completed research has been obtained, have been in the line of attenuated virus, which simply means that the specific agent in the prevention of any infectious disease is deprived of a portion of its virulence by being subjected to artificial cultivation, by increasing, perhaps, the temperature in which it develops, by a change in the atmospheric pressure, or a change in the oxygen; thus something is altered, and the virus, as, for example, the anthrax bacillus, loses its power to produce the full and virulent form of the disease. In some such way this organism, the bacillus of anthrax, which, under ordinary conditions and in full possession of its virulence will produce death within twenty-four hours in the lower animals, may be so changed in its power of producing the disease, yet retaining its power of growth, as, when introduced in large quantities into an animal's economy, to effect only a partial or no disturbance. This is an illustration of an attenuated virus. Another example is furnished by the method of treating the spinal cords of animals, particularly rabbits, dead of rabies. The cords of such animals contain the virus in its full intensity, and when subjected to certain conditions of drying it gradually loses its power to reproduce the disease, until at the end of two weeks it has no such power whatever. During these two weeks the strength of the virus is gradually *attenuated*. We must, therefore, exclude any consideration of Koch's material as an attenuated virus, for absolutely none of the results which follow the injection of this material either into man or the lower animals are followed by anything which we can in the least ascribe to the action of an attenuated virus.

Therefore, having shown that Koch's material is

neither an attenuated virus nor vaccine, what else can it be? We now come to the knowledge gained in years past in bacteriological research, a consideration of which enables us to give, without much hesitation, what seems to me a fair explanation of what this material is, and in order that you may clearly understand what I refer to, a few words in regard to the behavior of bacteria under cultivation is necessary. As most of you have seen, or will see, before you leave the school, the method of developing bacteria is, commonly speaking, by the employment of test-tubes filled for about one-third of their length with nutrient gelatine, or some material more or less favorable for the development of the bacteria under observation. This nutrient gelatine is somewhat of an amber color, and the method of planting the bacteria in the tube is by means of a platinum wire which has been sunk into a glass rod at one end and is free at the other. The free end is dipped into material containing the organism, and then immediately plunged directly through the centre of the nutrient material. The result of such a procedure is a visible line through the centre of the gelatine. If this is kept under observation for a short time, depending upon the time necessary for the development of the colony of bacteria, there is observed a gradual thickening of this line on both sides, and occasionally an elevation above the gelatine; then the further spreading of this colony of bacteria ceases, and does not go on any more at any time. For a long time it was difficult to explain why that occurred, but the knowledge which has come to us of late years furnishes a perfect explanation of why the colony does not grow farther out, and why its vitality is not destroyed. The bacteria take from the nutrient gelatine certain elements necessary for their development. They leave, therefore, the nutrient

gelatine in a state of partial chemical decomposition, and these unstable chemical elements come together and form new chemical compounds, all of which occurs directly along the outlines of this colony. Among these new chemical compounds have been found, during the last few years, an entirely new series of alkaloids of such unstable chemical nature that we are unable, in many cases, to separate them, to analyze them, or to secure their chemical symbols. The great element in this difficulty lies in the fact that most of these alkaloids are destroyed by a low degree of heat, and as we know, chemistry depends largely upon an extreme degree of heat for many of its analyses. Some of these alkaloids are not destroyed by such low degrees of temperature, however. A great characteristic is that they are inhibitory to the development of bacteria, and each variety of bacterium produces in a given nutrient material a special alkaloid or ptomaine, which is inhibitory to its further growth, but does not destroy its vitality. This, it seems to me, furnishes a very perfect explanation of what Koch's material must be, if the explanation of what goes on within the body after its use is correct. And the same idea is applicable not only in the disease tuberculosis, but there have already been announced researches suggesting the possibility of arresting the progress of other diseases in the same way. This is said to have been obtained in anthrax, and there is a strong hope of similar results in diphtheria, tetanus, and scarlet fever.

This material, it seems to me, can be nothing else than the ptomaines produced by the development of the bacteria of tuberculosis in some medium which permits of this alkaloid being separated out of the nutrient material after the bacteria of tuberculosis have produced it. I do not see how it can be anything else,

unless it be the ptomaine produced by some other form of bacterium, which has been found by Koch to act better in respect to the arrest of the development of that organism. Therefore, as far as our knowledge goes now, this is what this material seems to be. It is probably the ptomaine produced by the development of the bacilli of tuberculosis. Precisely in what nutrient material the bacillus is grown, or what is the precise method of its removal, it is, of course, impossible to say. There are certain things which could be said, which might furnish a *probability* as regards the methods of its production, but even if correct, no such announcement should at present be made.

As corollaries to what I have said, it follows most emphatically that this treatment is *not an inoculation.* An inoculation requires the introduction of something vital which will produce its kind, — will reproduce itself, in other words, — and this is distinctly what Koch's material does not do. The treatment is accomplished by a simple subcutaneous injection, not by an inoculation. It equally follows that Koch's material has absolutely nothing in common with a *lymph.* It is not a lymph; and if any of you will take the pains to look up the meaning of lymph in your medical dictionary, you will see how strongly the fact will be impressed on your minds that this material does not accord with the definition there given of lymph. The proper term has been suggested by Koch, himself, *paratoloid.* I do not know the derivation of the word, but it seems to be distinctly derived by analogy from names given to others of these new alkaloids, these ptomaines.

When I say that these ptomaines are the product of bacteriological development, do not picture to your minds that they are in any way the *excreta.* They are not excreta. They are simply the products coming

from the nutrient material, because the bacteria have absorbed some of the elements of the original material.

I have given you as far as I am able some sort of an idea of what this material probably is. Then comes the question as to what it probably does. To judge by the newspaper reports these effects are actually marvellous. I have seen one newspaper account of a man in the last stages of pulmonary tuberculosis who recovered under the doctor's eyes. It is hardly necessary to say that that sort of thing is not true. As far as my observation goes, extending over a superficial examination of some two hundred and fifty to three hundred cases, and the thorough examination of about thirty, and the treatment of something like twenty-six, the effects are double. In the first place they are local. By local I do not mean at the seat of the subcutaneous injection, but local effects at the seat of the pathological process; and there are general or systemic symptoms. The general symptoms consist, on the average, of a very marked rise of temperature. Most of these general symptoms occur, on the average, in from eight to twelve hours after the injection of the usual dose of this material. There may be a marked and sharp rise of temperature running up as high as 104°–105° F. There is a very great increase in the rapidity of the pulse and respiration. I have seen the pulse as high as 160 per minute without dangerous symptoms following. There is great headache, chills, and shivering lasting for some time, pains in the bones; and sometimes a very marked jaundice, not uncommon in surgical cases, but rather rare so far as I have observed in cases of pulmonary tuberculosis. These general symptoms last, on the average, about twelve hours after their appearance, when they all gradually subside, and the patient returns to his condition before the injection. There may be very marked depression in

temperature sometimes instead of a rise. One of the cases under my charge showed this. On last Tuesday, two hours after the treatment, the temperature fell 2½°, reached 95½° F. There was not the slightest other indication of anything going wrong with the patient.

There is in some cases, particularly in children, a very obstinate diarrhœa, nausea, vomiting, and occasionally collapse. But so far as my observation goes, the collapse is never great except in cases where the general powers were very much diminished before the treatment began. Nephritic disturbances have also been observed; albuminuria and symptoms of an acute nephritis, which subsided without apparently producing any permanent results. It must of course be remembered that the first case was only treated in October last, but so far as it has been possible to say, nephritic disturbances have disappeared. It is also a question whether these kidney disturbances were brought on by this material. Marked erythema is not uncommon and occurs, in distinction from icterus, in pulmonary cases, — as a rule the icterus in the surgical, and the erythema in pulmonary cases. I doubt, however, if this is anything like a hard and fast distinction.

In regard to the local changes which are observed, they are most prominent where the pathological change is visible to the naked eye. This necessarily, as you must know, is most prominent and most easily observed in cases of lupus, a virulent skin disease or skin tuberculosis, and the changes there observed are very marked, indeed. In this case also, the changes are limited to the locality of the pathological lesion; and, in lupus, these changes consist of a marked increase in hyperæmia of the part with an increase in the infiltration of the tissues. Crusts form upon

the ulcerating surfaces, which become thicker and thicker after each treatment, and finally fall off, leaving apparently healthy granulating tissue beneath. At the edges where there is no ulceration, the characteristic appearance is the formation of thick, heavy, dry, whitish scales, which gradually fall off as treatment goes on. This marked increase of activity is accompanied usually by a great amount of pain in the affected part, which comes on and lasts the same time as the general symptoms; so that the average patient is in about the same condition twenty-four hours after the injection that he was before it. These reactions, however, are not limited actually to twenty-four hours. There are what are called "delayed reactions," and these occur sometimes as late as forty-eight hours after treatment with a small dose. So, too, the subsidence of the symptoms is by no means constant. In a case which I have under treatment, injection was made on Saturday morning. Until one o'clock Monday morning there was practically no change from the normal; then the temperature was 103½° F.; then there was a gradual fall; and on Tuesday another rise to 102½° F.; again a gradual fall; and on Wednesday still another rise to 101½° F.; and only on Thursday did the temperature finally return to normal, thus giving a delayed reaction and a gradual subsidence.

But to come again to the consideration of the local symptoms; the next class of cases in which this material is employed, is in surgical tuberculosis, either of the joints or of the bones. In such cases, if for example they be similar to one which some of you may have seen in Dr. Warren's ward, to whom the irregular temperature chart spoken of above, belongs, with caries of the rib, the question may be raised as to the existence of tuberculosis and an attempt to settle the point may be the reason for injecting the patient. The

injection was followed by marked pain, great increase in amount of discharge, and there was an intensely disagreeable odor for a time. Whether the evacuated material contains the bacilli of tuberculosis, we do not yet know, but it will be possible to decide before long, because all the gentlemen who have been working in my laboratory are assisting in the work of systematic investigation of the cases in my charge. The marked increase in pain and amount of discharge are the especial things in surgical tuberculosis where there is any sinus at all. In cases where there are no sinuses, there is a marked increase in size of lesion and great pain, particularly inflammatory reaction, by that meaning heat and redness; and, finally, if the treatment has been persisted in for some time, a sort of necrosis apparently takes place about the tuberculous nodule, and in that way the tuberculous material can be let out by a simple incision, and emptied almost like a foreign body. If this material turns out to have the power, as it seems at present to have, of intimating the presence of tuberculosis by the production of either a general or local reaction, it is going to be of inestimable value to the surgeon and patient as a means of differential diagnosis; and here I should impress upon you very earnestly that the reaction spoken of as due to this material does not wholly refer to the reaction of the temperature. It is quite possible to have a chart following along the normal line, without any marked rise or fall. To have marked local changes going on and a local reaction, is just as important as the presence of a characteristic chart; and this fact has been much lost sight of.

Last, comes the consideration of what Koch's material does in cases of pulmonary tuberculosis. I am sorry to say that a large amount of the clinical material which is being collected in Berlin will be more

or less unsatisfactory in helping us to determine this particular question. The reason is that in the hospitals there they are overwhelmed by the number of applicants for admission for treatment; and in the excitement attendant, there have been a number of cases accepted, which will tend to throw discredit upon Koch's material, because they are in too advanced stages for treatment with any hope of recovery. It is quite necessary, to my mind, in order to have any knowledge of what this paratoloid can do in cases of pulmonary tuberculosis, to limit the experiments in the first place distinctly to a series of beginning pulmonary disease. Early apex catarrh, early localized disease in the bases are the ones to be selected for treatment, and as far as has been possible, such cases only have been selected for treatment at the Massachusetts General Hospital and the Boston City Hospital. In pulmonary cases, it seems to me, besides what we can actually observe, it is only fair to take for granted that a similar process goes on in the lung as in the skin, bones, and joints. In pulmonary cases there is certainly to be observed a very marked increase in the expectoration, a great and most distressing increase in cough, not invariably certainly; but these are the things which attract our attention. The marked increase of the physical signs during treatment and their subsidence after treatment are among the most interesting points. One of the patients of whom I have charge, showed this in a very interesting way by presenting no temperature reaction whatever, but he was able to point out and to trace upon his chest with the point of his finger precisely the limit of the lesions in his lungs. There was no deception about it, for only the day before a portion of the lung was discovered affected at the base, which the patient did not know anything about, and which

he marked out perfectly. That was a very marked thing, and struck Dr. Tarbell, in whose service he is, as one of the most interesting things he had seen thus far. One of the unfortunate things which occasionally occurs in pulmonary cases, is hæmorrhage. As a rule when this does happen it is severe. Whether it is actually brought on by the treatment is hardly an open question, it seems to me. It must come as the result of an intense local reaction going on and which certainly occurs in the pulmonary tissue as it does in the external forms of tuberculosis. Sometimes this hæmorrhage is almost uncontrolable, but it is to be said that it seems to occur only in cases of second and third stages of the disease. I do not know of a case where it has been brought on in the early stages, which is confirmatory of what I have just said in regard to the importance of treating only the early stages of pulmonary tuberculosis.

Then, as treatment goes on, as one injection follows another, the natural course of the curve of the temperature chart on the following days, is usually a sharp rise, a sharp fall, gradually diminishing in extent until it reaches the normal line. The sharp rise follows each injection, and diminishes in intensity if the same dose is continued: therefore, the usual practice is to increase the dose if the patient can bear it, that is, if the condition of the patient after the first injection is good. If, for example, the first dose was one-half milligramme, the second would certainly be one milligramme, the third one and one-half milligrammes, and so on. This is followed, as a rule, by a rise of temperature to the same or a greater height than after the first injection; but if the dose is not increased, the injection is followed by a diminution in the rise of the temperature, or no reaction at all. When no reaction follows a large dose, reaction being marked after similar ones

formerly, it is considered that the time for treatment to cease has come; and it is hoped to find, in cases of surgical tuberculosis where there has been an opportunity for discharge, that the tuberculous material has all been gotten rid of; or in cases of joint disease, as in one of the slides which I will show you, this tuberculous material will be surrounded by necrotic tissue. In the case of lupus the crusts fall off and leave a granulating surface ready to heal; in cases of pulmonary tuberculosis, the bacilli have disappeared from the sputum, the physical signs have been diminished, and the patient is sent out and kept under observation — the material has done all that can be expected of it; and after the treatment is omitted, the ordinary methods of nutrition are carried out. Now, the only point that remains, and which can only be decided as time goes on, is the permanence of these beneficial effects. As to their occurrence, there can be absolutely no question if one can believe the evidences of his eyes and ears. That lupus patches do diminish, cicatrize, cease in activity, there is no doubt at all; that pulmonary symptoms are immensely benefited and in a more easy way than occurs under any other treatment, there is also no question. The *only* question is the permanence of these good effects.

Then, of course, following out the investigation of such a question as this, one of the first things to be decided is as to what are the pathological or anatomical changes produced by this material; in this direction we are as yet pretty well in the dark. It is quite certain that the newspaper reports which have come to us in regard to Professor Virchow's speech in Berlin Friday night are very much exaggerated. The papers report him as saying this material scatters the bacilli. It is impossible for it to do anything of the sort, and I do not believe Virchow said so. Hyperæmia is a daily

occurrence. What I think Professor Virchow meant was to emphasize the necessity for extreme caution in the use of such powerful material as this Koch's paratoloid certainly is, and the necessity for watching the cases with great care.

The microscopic changes, so far as they have been followed out, seem to be a shrinking of the tuberculous tissue. After treatment by this material, the cells, instead of being spread out as usual, will be thrown much closer together, and the rods will be in between them.[3]

In some of the clinics it is asserted that the form of the bacilli change after treatment by this material. An attempt was made to show these changes to me; but I must confess that to see it requires a much sharper eye than I have. I do not believe there is any change in the organism itself that can be made out at present. The granular appearance is in no degree different from what always, or not infrequently, occurs in the expectoration from patients with cavities in the lungs. It is not uncommon to see this broken up appearance resembling the organism of tuberculosis, and there is little change in their appearance as it was shown to me. That is all that can be said in regard to the histology so far, and I have tried to say all that can be said in regard to the material. It may interest you to know something about its application and the methods adopted in using it.

In the first place, the back is selected for the injection of the material. Not certainly because it is easier to make an injection there, because the skin is very thick and tough, twice as much so as any other part of the body. But it is found that if there should be any local irritation at the point of injection, this part

[3] See plate in "Robert Koch's Heilmittel Gegen die Tuberculose." Erstes Heft, S. 27. Berlin and Leipzig, Dec., 1890.

of the back between the scapula and vertebral processes is the place upon which the least pressure is apt to be exerted; because when the shoulders are thrown back there is a little hollow there, and most persons lie on one side and not directly on their backs. The subcutaneous injection could be made anywhere but for this reason. In Berlin the back is prepared for injection in the first place, by being thoroughly washed with soap and water with a hand brush; then, just at the time of operation, the surgeon's hand is placed upon the back, the skin is stretched and thoroughly scrubbed with a solution of 1-20 carbolic acid. This is the only preparation I saw used in Berlin.

In this city, at the Massachusetts General and City Hospitals a little more technique is followed out. The preparation of the back of the patient is begun the night before by the application of antiseptic poultices. The hands of the operator just before handling the needle are very carefully sterilized by first washing them with soap and water, then by the use of corrosive sublimate (in my own case I use about 1–5000), and this is finally washed off in carbolic acid. It is pretty severe treatment for the skin of the hands, but it is about the only way in which one can secure safety in such cases as this. The syringe with which the injection is made is similar to the one shown. It consists of a rubber bulb with a hole which can be stopped up with the thumb, and a valve turned by the other thumb and finger, the cap attached to the valve fitting closely in the ground edge of the glass tube. In the recent modifications of the syringe, the needle fits on the other end of the glass tube. The older form has an extra shield, on which the needle fits. The fluid is drawn up by opening the valve, freeing the bulb of air, plunging the needle into the material, and, when you have enough, closing the valve.

The syringe used for the treatment is made to hold one cubic centigramme of fluid, and is also divided very exactly into tenths of a cubic centigramme. The syringe, itself, is sterilized before and after each patient is injected, in the first place with a half per cent. solution of carbolic acid in doubly distilled water, which is drawn up and down several times through the needle and syringe itself. The syringe is washed on the outside. The whole of the carbolic acid is washed off both inside and outside by as nearly absolute alcohol as chemistry can obtain. The nearest approach to that which is easily obtainable is Squibb's absolute alcohol.

It is an interesting point for you to know that so much is said about, and so much is done with material contained in a flask certainly not any higher than one and a quarter inch, containing five grammes of fluid. Koch's material is disposed of in Berlin in flasks containing only five grammes. By the dilutions, however, to which this material must be subjected, there are, of one milligramme doses, 5,000 in each flask. The dilution is accomplished by taking one-tenth of a gramme of the material and adding nine-tenths of a gramme of distilled water, giving one part in ten, and one gramme of fluid; to this is again added nine grammes of distilled water, giving one part in 100 or ten grammes of fluid; and again 90 grammes of distilled water, giving one part in 1,000 or 100 grammes of the fluid. This is the regular standard method of dilution, and it can be varied as one chooses. A special point in regard to it is that the original material keeps indefinitely. After it has been once diluted, however, it decomposes within a moderate degree of time if one uses distilled water alone, and decomposition with the consequent loss of material can be guarded against by making the dilution with a half per cent. aqueous solution of carbolic acid. The method I have adopted is to make the dilution with half per cent. solution of carbolic acid, divide

the resulting 100 grammes of solution in sterilized test-tubes, stoppered with absorbent cotton and covered with rubber caps. These are sterilized after each opening for use, in a steam sterilizer for five minutes after the steam has begun to pass. The sterilizer I use is the Arnold sterilizer. It is more effective than the ordinary one of Koch's, and the steam in it is under a slight degree of pressure and is raised to 102° to 103° C., so that sterilization is accomplished more quickly than in Koch's. It has been my experience, as well as that of those in Berlin, that by doing this, after each opening of the test-tube, the material keeps practically for a fortnight, so that a great deal of unnecessary and tiresome detail can be avoided.

It may be of interest to you to hear a very brief account of a few of the cases that I saw, which furnished a basis for the faith that I have that this material of Koch's is the introduction to us of a change in the medical treatment of disease, of which we have as yet no conception. I believe that this is only one of a series of discoveries of equal importance which will practically revolutionize the practice of medicine before you gentlemen are twenty years older. Further discoveries are more a question of time and endowment of research than of brains. In the first place this result is not a surprising thing to me. It has been in the air for several years. The whole knowledge which we have been gaining in regard to ptomaines, and the growth of bacteria, in various nutrient-media, has pointed to something of this kind, and it is extremely curious also to note that, as far-fetched as it may seem, Pasteur's laboratory is remotely responsible for this great discovery. The reason for this you will easily understand, when you are told that when the bacillus of tuberculosis was first discovered, the only material upon which it would grow was sterilized blood-serum.

It was extremely difficult to get good results. The study of the bacilli in blood-serum could only be carried on by men who had all the apparatus necessary, and they were able to carry this study to only a limited extent. But some three and a half years ago there was announced from Pasteur's laboratory the fact that the addition of a certain per cent. of glycerine — six to eight per cent. of pure glycerine — to the ordinary nutrient media (nutrient-gelatine, nutrient-agar-agar), furnished as perfect a soil for the cultivation of the bacilli of tuberculosis as we could possibly desire. In such materials it developed very quickly, much better than in the ordinary sterilized blood-serum; and it was in this way only that the possibility of carrying out researches upon this organism was placed before so many people. At that time I made a prediction foreshadowing something of this kind. I was asked to go to Worcester and address the medical society there, and was permitted to choose my own subject. I chose Tuberculosis, and carried there a number of cultures of the bacilli in nutrient glycerine-gelatine, and nutrient glycerine-agar, and there I made the assertion that for the first time we were justified in hoping for some such result as has come, *because* of the increased ease with which the bacillus of tuberculosis could be studied.

Now, in regard to the cases I saw. The most interesting, were two of apex catarrh which had been under treatment for about six weeks. There had been marked dulness at both apices, of both cases I think, certainly in one. Numerous moist râles were present and bacilli of tuberculosis were found in the sputa. After carrying on the treatment for six weeks, practically all of these signs had disappeared. There were no bacilli in the sputa, no râles, and although diminished resonance was still present, dulness had entirely disappeared. Reaction had

ceased and then the bacilli had disappeared. In the other case there were a few râles left, and dulness was very much diminished. No bacilli in the sputa. These cases were not completely well of course ; but so far as the physical examination showed, so far as the general condition of the patient was concerned, they had improved beyond anything which I had ever seen before in any case under treatment.

Then as an example of a different class, I saw a case of chronic pleurisy, accompanied by night sweats, dry cough, loss of appetite, where there had been no expectoration. After three or four treatments there was a great amount of expectoration and a large amount of bacilli. That was one of the cases in which a pulmonary tuberculosis had apparently been developed, and this chronic pleurisy was really a tuberculous pleurisy.

Then another very interesting case was one of incipient phthisis, containing many bacilli in the sputa. The treatment began with an injection of two milligrammes, followed by an injection of five milligrammes. The first treatment being followed by a very marked temperature reaction, but the second injection of five milligrammes, — a very large dose for such a case, — was followed by absolutely no change whatever. In three days afterwards a third injection was given, this time also of five milligrammes, and then reaction went on. There was a gradual diminution of the number of bacilli.

One of the most tremendous cases which I saw was one of ulcerative lupus of the face, back, and arms. It had been under treatment for six weeks, the dose running from one milligramme up to the last one given on the 22d of November, eight milligrammes, and no reaction following the last three injections. The ulcerations of the lupus tissue had completely stopped, and they were practically cicatrized before I came away.

Another striking case was one of lupus of the face, where the treatment had been going on for about eight weeks. In this case very large injections were made, the first was one centigramme of a one per cent. solution, — ten milligrammes of the material. This is a very large dose indeed, and even three centigrammes of this one per cent. solution were used. The result in that case was something nearly marvellous. In eight weeks the whole face was cicatrized; there was no reaction, no elevation of temperature, no swelling in the parts; and if one ever saw anything, one saw healthy skin amounting to at least two square inches in area, as islets among the lupus nodules.

Another case was one in which the diagnosis of tuberculosis was made because of the reaction to treatment by this material. There was a sprained (?) ankle, at which appeared a nodule, incision was made and the whole thing was taken out as if it was shelled out. The surgeon could almost follow a line of demarcation as a result following treatment.

The most striking case of all was one following nephrectomy in a boy of thirteen, who had had an abscess of the kidneys. Incision was made and the whole evacuated and cleaned out, and everything had healed up perfectly. The cicatrix was solid. The boy was gaining in weight, and was about to be discharged, when as a matter of interest some of this material was injected. The reaction following was very marked, and after three or four injections, I do not remember exactly how many, there appeared in the cicatrix a tuberculous nodule about the size of the tip of my little finger. This dropped off and was proven to be tuberculous, and the cicatrix healed. There was no further reaction to treatment, and the boy went out, I believe, without any signs of disease. If the tuberculous material had remained within the cicatrix the chances are that something might have occurred to start the nodule

into activity when it could not reach the surface and would be forced into the abdominal region.

It may also interest you to know something of the doses employed in Berlin; and to that end I read you some extracts taken from my note-book; the doses are given in milligrammes of the *undiluted* material:

(1) M., phthisis, with cavities in the left lung.

Nov. 20	1 mg.	Nov. 26	4 mg.
" 21	2	" 28	10
" 23	5	Dec. 1	10

(2) T., lupus, eight weeks under treatment, ulceration almost stopped.

Nov. 4	1 mg.	Nov. 20	1.5 mg.
" 6	1	" 22	2
" 9	1	" 24	1
" 12	1	" 25	2
" 16	1.1	" 26	4
" 18	1.4	" 27	8

No reaction after the last three injections.

(3) S., osteomyelitis, scraped out, and then tuberculosis of the lungs suspected, proved by the injections and the physical signs.

Nov. 21	2 mg.	Dec. 3	5 mg.
Dec. 1	4	" 4	5

(4) T., parotid abscess (control case).

Nov. 26	1 mg.	Nov. 30	18 mg.
" 27	5	Dec. 3	20
" 28	10	Dec. 4	30
" 29	14		

No reaction after any injection.

(5) B., tuberculosis of ankle.

Oct. 12	1 mg.	Oct. 16	3 mg.
" 13	2	" 18	4
" 15	2		

From November 3d to 7th, erysipelas.

Nov. 13	8 mg.	Nov. 21	9 mg.
" 19	10		

Operated upon on 21st.

Nov. 25	12 mg.	Nov. 30	28 mg.
" 27	20	Dec. 3	30

No reaction.

(6) F., —— of knee, tuberculous (?)

Oct. 17	5 mg.	Nov. 13	10 mg.
" 18	10	" 18	11
" 21	10	" 22	20
" 23	10	" 26	40
Nov. 1	10	Dec. 2	50
" 8	2	" 3	50
" 10	5	" 8	50
" 12	10		

No marked reaction at any time, except on October 21st and 23d and November 1st. Between October 21st and 23d, the temperature was 36.3° C., or subnormal.

As good a picture of what may occur as can be given is furnished by the notes of the first injection of the case of lupus, the photograph of which I have just shown you upon the screen, I will therefore read them to you. They were taken by Dr. Abbot, with whom I was, at the bedside.

The case was one of sixteen years' standing, extending over the nose, both cheeks, and under the chin, passing into the mouth and attacking the gums, pharynx, and larynx, — the vocal cords were almost destroyed. The general appearance before the first injection was that of an ordinary subacute process.

December 9, 1890, 9 A. M., received one milligramme injection. At 4.30 P. M. the general appearance of the lesions was that of an acute process, there was shivering as in an ague fit, the face was intensely red, the reddening being confined to the diseased parts, with the healthy skin but little altered. There was serous exudation from several ulcerating points and from the angles of the mouth. There was headache, pains in the joints, a diffuse exanthem upon the arms and breast. Temperature 38.5° C. (Westphal says that according to his observation, the chills occurring after

the first or second injection average two and one-half hours in duration.)

On the following morning the above condition was but little altered. Temperature 38.2° C. at 9 A. M. There was still slight exudation and some swelling, but the tension was much diminished. The patient slept poorly but feels better than he did in the night. Persistent, irritant cough has appeared, perhaps owing to the action of the material upon the larynx. The reaction is passing away much less rapidly than is ordinarily the case. The exudate is beginning to dry, and is quite markedly so upon one of the larger spots of ulceration.

The general condition of the patient on the following day was much improved. Temperature gradually sinking to normal, the thickness of the diseased skin much diminished, as well as the reddening. Over that portion of the diseased processes which was fairly smooth before the injection, there are now numerous evenly scattered dry, whitish scales. (This is the usual result at the edges of the lupus patches after treatment with Koch's material.)

The following morning (December 11) the general condition of the patient was sufficiently improved to admit of a second injection of one milligramme of the material. At the time of the injection, with the exception of the dry scales on the smoother portions of the process, the local condition differed but little from that at the time of the first injection.

This, gentlemen, concludes what I have to say upon this subject this evening. I thank you for your attention, and trust I have been able to explain some of the points in regard to it to your satisfaction.

NOTE. – My hearty thanks are due to Drs. Klemperer and Westphal, for the extreme courtesy shown to Dr. Abbot of Johns Hopkins University and me, and for the facilities placed at our disposal for observing the cases under their care.

H. C. E.