PROFESSOR KOCH'S REMEDY FOR TUBERCULOSIS. LECTURE

KOCH'S TREATMENT OF TUBERCULOSIS.

Delivered at King's College Hospital, December 3rd, 1890.

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GENTLEMEN,—Having just returned from a visit of a few days to Berlin, where I have had an opportunity of witnessing Koch's treatment of tuberculosis, I will relate to you some of my impressions regarding it. I need not now describe the method of procedure further than to say that it consists in the injection of a few drops of a dilution of Koch's fluid into the subcutaneous tissue, the part usually selected being the back between the scapulae or the lumbar region. The effects of this treatment upon tubercular disease are simply astounding. Take, for example, the case in which its results can be most readily observed—in consequence of the superficial position of the affected part—lupus of the face. I saw in Berlin a patient with extensive lupus of the cheek, in whom an injection such as I have described had been performed two days previously. The cheek was enormously swollen and red, and the affected part of the skin covered with crusts of dried serum which had exuded as the result of the intense inflammation that had taken place. Meanwhile, no inflammation had been produced in any other part of the body. It is only the part affected with tubercle that is in the slightest degree influenced. Similar inflammatory effects are produced in other tubercular affections, wherever they may be situated. Thus in strumous glands of the neck, swelling of the glands, with redness of the skin over them, and pain, follow the injection. In gelatinous degeneration of the synovial membrane of the knee the same thing occurs. Again, in tubercular disease of the larynx, where also we have the opportunity of seeing what takes place, corresponding inflammatory changes are observed. But if the patient is affected with any disease other than tuberculosis, such as cancer or syphilis, no more effect is produced than on a healthy person. Tubercular tissue only is affected by the treatment. Meanwhile the effects on the system generally are scarcely less striking than the local ones. An injection which in a healthy person would produce no symptoms whatever is, in a tubercular subject, followed after a few hours by a more or less severe, though transient, feverish attack, characterised usually by pains in the limbs, shivering, prostration, nausea, and perhaps vomiting, while the temperature undergoes a considerable rise—it may be even to 105° or 106° F. The quantity of the material which produces these effects is extremely small. One-thousandth of a gramme of the fluid is the usual dose for the first injection in a case of phthisis. Now, Dr. Koch informed me that the undiluted fluid contains probably only about a thousandth part of the really active ingredient. If, therefore, one-thousandth of a gramme of the fluid is employed, only a millionth of a gramme of the active substance is used; yet this almost inconceivably minute quantity, diffused throughout the circulation of the human body, gives rise to these remarkable changes. But no such results occur in persons affected with disorders other than tubercular, such as cancer or syphilis. A precisely similar train of febrile symptoms may, indeed, be induced in persons who are not affected with tubercle by using a sufficiently large dose of the fluid; but for this purpose about a tenth of a gramme is required, or a hundred times the quantity that exists in the first injection in a case of phthisis. Thus, in its general, as well as in its local, effects this substance picks out and renders manifest tubercular disorders as contrasted with other conditions. It thus comes to have the highest value for diagnostic purposes. A case occurred lately in Berlin, in which there was a doubt whether a tubercular affection of the larynx was syphilitic or tubercular; an injection with the fluid cleared up the diagnosis at once in favour of the latter hypothesis.

The substance seems to be wonderfully searching in its effects upon tubercle. In a house which I visited, a young medical man

had an injection performed upon him as a matter of experiment, not having the slightest suspicion that he was the subject of tubercle. A violent feverish reaction followed, which led to a careful examination by a physician, and this revealed a slight but unmistakable disease of the apex of one of the lungs. A similar result occurred in the case of a lady with phthisis, who had formerly been under treatment elsewhere for a small tubercular ulcer of the larynx in the inter-arytenoid fold of mucous membrane. This ulcer had been for six months completely healed after scraping and the application of lactic acid; but after injection with Koch's fluid, a red granulation made its appearance, projecting from under the left vocal cord, showing that tubercular disease was lurking where it had not previously been suspected to exist. I also saw cases where tubercular joints had been excised several months before, and all had appeared perfectly sound; but injection being practised on account of fresh tubercle elsewhere, the scar and surrounding parts became red, swollen, and painful, whereas scars of other kinds are absolutely untouched by the treatment. This would appear to indicate that some remnant of tubercular affection was present in the seat of excision, although no other means at our disposal would have indicated its existence.

But while Koch's fluid has this searching diagnostic value, there can be no doubt that it has also a powerful therapeutic or curative influence. In lupus of the face, for example, which may have long obstinately resisted other means of treatment, the crusts that form on the affected part as the result of the injections fall off in due time, leaving a more or less completely sound scar. This has been known to result from a single injection, although more frequently a repetition on several occasions is required.

In tubercular disease of the synovial membrane of the knee-joint the swelling caused by the injection soon subsides, and leaves the part smaller than before. The same thing occurs after each injection, and though I had not the opportunity of seeing any cases of this kind in which a completely natural state of things had been brought about, I was informed that such had been observed. I also learned on trustworthy authority that patients in the early stage of phthisis had, under the treatment, lost all their symptoms. The purulent sputa, after diminishing in amount, had become mucous in character, at the same time losing the tubercle bacilli, and had finally ceased entirely. Night sweats had disappeared, progressive loss of weight had given place to gain of flesh, while the physical signs of the disease had vanished.

But, it may be asked, how far are these effects likely to be permanent, and what limits are to be anticipated to the curative agency of the method? In seeking for an answer to these questions, let us return to the case of lupus of the face. It is found that some parts of the diseased tissue lose their vitality altogether under the violence of the local action, and are discharged as sloughs. There are other situations where necrotic portions may be so disposed of. I saw a patient who had coughed up from his larynx a considerable piece of necrosed tissue, and dead portions of lung substance may be expelled with the sputa. But there are many situations in which parts deprived of their vitality by the remedy cannot be thus discharged externally, and I have seen it argued in print, and heard it maintained in conversation, that it is impossible under such circumstances for the dead portions of tissue to be got rid of. To you, gentlemen, such an idea would probably hardly occur. It is now many years since I observed that dead portions of tissue, if preserved from septic agency, are not necessarily separated *en masse* from the living body, but are gradually absorbed. This it was that led me to employ the catgut ligature, which, though composed of dead tissue, is eliminated by absorption. The tissue of tubercular parts is not irritating in the sense in which a piece of putrid slough is irritating. It would seem that the tubercle bacilli give rise to the production of some poisonous substance which modifies the nutrition of the parts in which they grow; but the tubercular tissue which arises from this cause is not incapable of absorption. This we know from ample experience. Thus in the ordinary strumous form of antero-posterior curvature of the spine the bodies of the vertebrae have become so softened under the influence of the growing tubercle bacilli that they have yielded beneath the weight of the upper parts of the body. But if a patient with such an affection is brought under our care before abscess has developed, even although the curvature is already strongly pronounced, we have only to enforce the strict maintenance of the recumbent posture, so as to place the affected part at rest, giving at the same

time good nourishment with suitable tonics, in order to ensure a spontaneous cure. The tubercular tissue and its contained bacilli alike disappear. And there is no reason *a priori* for supposing that the death of any portion of tubercular tissue through the agency of Koch's fluid would render it unfitted for absorption. Hence this theoretical argument against the possible efficacy of the treatment falls to the ground. As a matter of fact, it is completely refuted by experience. In those portions of a lupus patch where there is no actual sloughing as a result of the injections, but only inflammatory swelling, the tubercular tissue gradually disappears, although there can be no doubt that necrotic portions are scattered through its substance. Similarly in laryngeal disease where no ulcers are present, but merely tubercular infiltration of the affected structures, the swelling has been observed to subside steadily under repeated injections without the occurrence of either sloughing or ulceration.¹

While the tubercular tissue is got rid of by this treatment, it appears to be clearly established that the tubercle bacilli are not killed by it. It does not, however, at all follow that the tubercular disease may not be cured, although the bacilli are not directly affected. If the special diseased tissue which they inhabit is eliminated, the bacilli will be turned adrift among the healthy tissues in the vicinity, and may be quite unable to maintain their ground there. In a public hospital like this we are doubtless all of us frequently taking tubercle bacilli into our bodies; yet even in those who are hereditarily predisposed to tubercle, the healthy tissues wage successful war against the microbes, unless some accidental circumstance gives them an unusually favourable nidus for their development. It is the living tubercular tissue on which Koch's remedy directly operates; yet the bacilli are affected indirectly. But what shall we say of caseous masses and sequestra in which tubercle bacilli are lodged? Koch's fluid cannot touch such bacilli, directly or indirectly, and the necrotic masses may remain as sources of future infection, like potent inoculations of a tubercle culture. In many cases, no doubt, we may combine surgical procedure with Koch's treatment, and operate, we may hope, with greater success than heretofore; because while we as surgeons clear out the dead infecting masses, Koch's injections will cure the surrounding living tubercle. But there are, I need hardly say, situations where the surgeon's knife cannot penetrate; and when extensive caseation or necrosis affects parts thus inaccessible, and where spontaneous expulsion outwards is impossible, Koch's treatment in its present form affords little prospect of cure. Perpetual fresh injections might, indeed, be combated by often-repeated injections. But as the absorption of extensive necrotic *débris* must be at the best a most tedious process, the treatment would, under such circumstances, have to be indefinitely protracted. What we here want is immunity from tubercle infection. If we could gain that; if, while the existing tubercular tissue was destroyed, the healthy tissues round about were rendered incapable of affording growth to the bacilli, or, rather, capable of resisting their development, the caseous or necrotic masses, with their bacilli in them, would remain harmless as sources of further infection, and the tubercular disease would be definitively cured. That is what we want in order to make this treatment perfect. Now, Koch himself has thrown out in a footnote to his paper published in the *Deutsche medicinische Wochenschrift* of November 13th the possibility that immunity may result in consequence of the treatment. Hitherto, however, it does not seem to have been attained. We read of cases—in the *Lancet* of last week there is one reported—where, lupus having been apparently cured by a course of injections, a recurrence had taken place. We can well understand that if immunity has not been established, some necrotic piece remaining unabsorbed with its living bacilli may start the disease afresh.

The immunity of the whole system, which is so desirable, does not therefore seem as yet to have been attained. In the concluding passages of Koch's address on Bacteriology at the International Medical Congress, he revealed the fact which astonished the world, that he had succeeded in finding a substance which, when injected into tubercular guinea-pigs, cured them. Before mentioning this wonderful curative effect, however, he stated that the substance in question produced immunity of these highly susceptible animals against inoculation of tubercle.

The immunity, gentlemen, seemed at the time a less striking thing than the cure, because it was only in harmony with what we had already known in the case of diseases such as anthrax and chicken cholera as the result of Pasteur's "vaccinations." But the immunity

is that which we now long for. It has not been attained in man as it has in the guinea-pig. Why should there be this difference between the guinea-pig and man as regards immunity? It strikes me it may, perhaps be due to the fact that the guinea-pig is capable of taking much larger doses of Koch's fluid without bad effects. In a healthy guinea-pig 2 cubic centimetres—that is to say, practically, 2 grammes—of Koch's fluid undiluted produce no effect in the way of general reaction, whereas in a healthy man 0.2 cubic centimetres, just one-tenth of the quantity, would probably cause serious febrile disturbance. Koch himself, having experimented upon guinea-pigs, tried, like a hero, the effect of an injection upon himself. He employed 0.25 cubic centimetres, which, as we have seen, would have produced in a guinea-pig no general disturbance at all, and the results in him were serious, and, indeed, alarming. A guinea-pig, then, will take fully ten times as large a dose as a man to produce the same effect upon the general system. But if we consider what the weight of the guinea-pig's body is as compared with that of a man, we find that the guinea-pig requires, weight for weight, at least 1,500 times as much of the fluid to produce any effect upon the general system. And it seems to me very likely that the immunity in the guinea-pig results from the comparatively large dose of the fluid which it receives. If this be so, it might perhaps be possible to produce immunity in man also, if we could sufficiently increase the dose of the remedy. Now it is a remarkable circumstance with regard to the injections in tubercular patients that, beginning with a small dose, one-thousandth of a gramme it may be, producing considerable fever, the fever having subsided, twice as much may perhaps be injected next day without causing as much fever as resulted from the first injection; and in the course of two or three days a considerably larger quantity may be used without producing any general effect whatever. It has been known that, after three weeks of the treatment, 500 times the original dose has been borne. How is this to be explained? There seems to be two conceivable explanations. One is that there may be an acquired tolerance of the remedy, the system being accustomed to it, as it does to morphine or to arsenic. The other is that the fever is caused, in part at least, by the inflammation of the tubercular tissue induced by the remedy, and that as the tubercular tissue is progressively eliminated, there is less and less tissue to be inflamed, and therefore less fever. I confess I cannot think that the latter is the true explanation. It seems to me inconceivable that, in a patient with a considerable mass of tubercular disease in the lungs, the tubercular tissue can be reduced by one-half in the course of twenty-four hours. Yet this it seems necessary to assume in accordance with the hypothesis. It is also a significant fact that the degree of fever caused by the first injection is by no means strictly proportioned to the amount of tubercular disease present in the patient. It may be said, indeed, that we have no analogy for such rapid accommodation of the system to such a powerful remedy. But the principle of acquired tolerance is familiar to us, while the remedy is of a totally novel character. Acquired tolerance, then, seems to me to be by far the more likely explanation. If this be the true state of the case, it seems to point to the possibility that the tolerance might be carried still further, and brought up to a considerable higher degree than obtains in the healthy subject. We have seen that the fever which is induced in tubercular patients by Koch's remedy is identically similar to that which is caused in healthy persons by larger doses. As regards the fever, unlike what occurs in the local phenomena, the tubercular patient differs from the healthy in degree, not in kind.² It seems, therefore, *a priori* not improbable that increased tolerance might be induced in the healthy person also, and that in the tubercular, if instead of stopping short at the dose ordinarily borne by the healthy, the quantity were pushed steadily further and further, a degree of tolerance might be attained which might be attended with immunity. If this has not been already attempted, it seems to me worthy of trial.

But there is another line of inquiry from which I cannot help hoping for good results. Through Dr. Koch's great kindness I had the opportunity of penetrating into the arcana of the Hygienic Institute of Berlin, and seeing most beautiful researches being carried on in that institution, of which Koch is the inspir-

² It would appear from recent publications that cases now and then occur in which little or no fever is produced by the ordinary injections, in spite of the presence of a considerable amount of tubercular disease. Vide *Deutsche medicinische Wochenschrift*, Dec. 4th, 1890, p. 1134.

¹ Vide Lublinski: *Deutsche med. Wochenschrift*, Nov. 27th, 1890.

ing genius. I saw things which, while they excited my admiration, made me also feel ashamed that we in this country, from one circumstance or another, are so greatly behind our German brethren. The researches to which I desire specially to refer are still in progress, and fresh facts are accumulating day by day. As they have not yet been published, I am not at liberty to mention details, but there can be no harm in my saying thus much, that I saw, in the case of two of the most virulent infective diseases to which man is liable, the course of the otherwise deadly disease cut short in the animals on which the experiments were performed, by the injection of a small quantity of a material perfectly constant in character, an inorganic chemical substance as easily obtained as any article in the materia medica. And not only so, but by means of the same substance these animals were rendered incapable of taking the disease under the most potent inoculations; perfect immunity was conferred upon them. I suspect that before many weeks have passed the world will be startled by the disclosure of these facts. If they can be applied to man—though our experience of the different behaviour of Koch's fluid in guinea-pigs and in the human subject makes this a matter of uncertainty until tested by experiment—but if they can be applied to man, the world will be astonished, and the beneficence of these researches will be recognised on every hand. At the present time Koch is engaged in the earnest endeavour to produce his remedy for tubercle by some process which could be divulged without the risk of the public being supplied either with material useless from its inertness, or, on the other hand, with deadly poisons. Koch, I believe, would not have published his method at all, had it not been for great pressure brought to bear upon him, until he could have produced it in a form capable of being revealed in every detail. It is nothing but the fear that, by publishing now the precise mode of preparing this material, he might do immense harm instead of good that prevents him from making it known; and I must say that the carping against Koch on account of what is spoken of as a "secret remedy" can only proceed from absolute ignorance of the beautiful character of the man. But if it should so happen that, as with the other diseases to which I have referred, so with tubercle, complete immunity should be obtained by means of some inorganic chemical substance which anyone can prepare, then would be achieved the complete triumph of the treatment of tuberculosis. And, for my part, I rejoice that we are permitted to look forward with hope to that glorious consummation.

SOME ASPECTS OF PROFESSOR KOCH'S TREATMENT OF TUBERCULOSIS.

BEING AN ADDRESS DELIVERED IN THE WARNEFORD HOSPITAL,
LEAMINGTON, ON DECEMBER 6TH,

By I. BURNEY YEO, M.D., F.R.C.P.,

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to King's College Hospital.

[DR. BURNEY YEO, after some introductory remarks, expressed his thanks to Professors Ewald and Fraenkel, and to Professor von Bergmann's accomplished assistants, Drs. Nasse and Roth, and added that he had had the advantage of the companionship and co-operation of Dr. Bowles, of Folkestone, during his recent visit to Berlin.]

Our first visit, he continued, was to the clinic of Professor Ewald at the Augusta Hospital, and it was here—thanks to that eminent physician's characteristic courtesy and kindness, as well as to his thorough and painstaking methods—that we were able to make ourselves familiar with the effects of the injection of Koch's fluid in many cases of phthisis, as well as in other diseases. Here, however, as well as elsewhere, it was scarcely possible, so short a time had the patients been under treatment, to observe that any actual curative changes had taken place.....But it was exceedingly interesting and important to note the action of Koch's injections in cases in different stages of this disease.

Advanced Cases of Phthisis.—First, with regard to its action in advanced cases. In some of these cases the reaction to this agent is very severe; a high degree of fever is excited, and occasionally very serious symptoms are observed. In one case I had the opportunity of seeing, after an injection of 2 milligrammes, total collapse occur, associated with violent diarrhoea; and camphor and ether had to be injected to rally the patient. After a second

injection no collapse occurred, and she bore a third injection of 4 milligrammes with only the usual reaction, namely, rise of temperature and pulse (to 140) and much flushing of the face.....This case, I have recently heard, is doing well, notwithstanding the serious symptoms attending the first injection.

In another case of advanced phthisis in this clinic, a woman with a cavity in the upper part of the right lung, and with a very cachectic aspect, much cerebral excitement followed the second injection of 2 milligrammes. She became delirious during the strong reaction that followed, when the temperature rose to between 104° and 105° F.

Early Cases of Phthisis.—In a case of phthisis in the early stage, with strong reaction, hæmoptysis occurred six hours after the injection, though no hæmorrhage from the lung had occurred before.

The Dose necessary to Produce Reaction.—As illustrative of the dose necessary to insure reaction in cases of pulmonary consumption, we observed a case in which no reaction occurred after the three first injections of 2, 3, and 4 milligrammes respectively; but, when 5 milligrammes were injected, the characteristic reaction appeared. We also saw a case of chronic phthisis that had been in Davos for two years, and failed to react to doses of 3, 5, and 8 milligrammes respectively; and there were one or two more cases of undoubted chronic phthisis with bacilli in the sputum that had not reacted to the injections that had been made up to the time of my last visit. Another case in Professor Ewald's clinic that yielded no marked reaction after injection of ordinary doses was that of a highly neurotic young man, with tubercle bacilli in the expectoration, but no well-marked pulmonary physical signs. This was also the case with a gentleman who was in a private sanatorium in Berlin, and whom I had seen in London so long ago as September, 1887. In this case there were evidences of a good deal of pleural thickening, and probably extensive fibroid changes in the left lung. He may, however, have reacted by this time to larger injections.

Another case that reacted very slightly to the injections was that of a medical man I saw in a private clinic with Professor Fraenkel. He had been attacked with tuberculous disease of the right lung twelve years ago; the disease was arrested at Meran, and he remained well for ten years. Two years ago he had a slight return of the former symptoms, with some catarrhal signs over the right apex, but his general health remained good. In this case, also, the very slight reaction might be due to the fact that fibroid changes had occurred in the neighbourhood of the old disease, and that there was very little tuberculous tissue accessible to the circulatory current. Koch has pointed out that his fluid has no effect on necrotic cheesy masses.

There is a case in King's College Hospital now, under my colleague Dr. Beale, with a cavity in one lung, who did not react to the first two injections of 2 and 4 milligrammes respectively, but he has reacted to one of 8 milligrammes.

Laryngeal Tuberculosis.—In Ewald's clinic, as well as in von Bergmann's and in the private clinic of Professor Fraenkel, we saw several cases of laryngeal tuberculosis under treatment. It had been feared that, owing to the swelling and redness observed in cases of lupus, this treatment would be attended with much inconvenience, if not serious risk, in cases of tubercle of the larynx; but, somewhat strange to say, this does not appear to be the case. In the case of laryngeal tubercle we saw in Professor Ewald's clinic there were also physical signs of deposit in the apex of the left lung. The injection produced no oedema of the larynx, and only slight dyspnoea occurred during the reaction. The voice was improved. In von Bergmann's clinic we saw a man with laryngeal tubercle, who had much dyspnoea during the reaction, and being seized with a severe fit of coughing he coughed up a bit of necrotic tissue, in which giant cells were found on microscopic examination. In this case also the voice was much improved. We were also shown a man in this clinic with tubercular deposits and ulcerations of the mucous membrane covering the hard palate; and it was most remarkable to see how, under the influence of the remedy, the deposits could be seen melting away and leaving clean excavations behind. Professor Fraenkel showed us a male patient in whom he had, as he thought, completely removed by the curette a tubercular deposit on the posterior wall of the larynx, but he still reacted to the injection, and it was observed that the excavated part had become swollen, and still, doubtless, contained tubercle. He also showed us a case in which the tubercular deposits in the larynx were disappearing under this treatment.