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[Editorial in the MEDICAL AND SURGICAL REPORTER, September 6, 1890.]

PREVENTIVE INOCULATIONS AGAINST TUBERCULOSIS.

At the recent meeting of the International Medical Congress, in Berlin, Dr. Robert Koch made an address in which he asserted that he had discovered a method by which animals ordinarily very susceptible to contract tuberculosis from inoculations of the bacillus were made capable of resisting such inoculations. The details of his method he did not make public. Stimulated apparently by this announcement, which is calculated to attract widespread attention, Drs. Grancher and Martin, of Paris, announced in the *Bulletin Medical*, August 20, 1890, that they also had devised a method by which these results could be obtained.

In this number of the REPORTER Professor Samuel G. Dixon, of Philadelphia, presents a short article in which attention is called to the fact that a year ago—*Medical News*, Philadelphia, October

19, 1889—he had proposed the lines upon which preventive inoculations against tuberculosis might be expected to be successfully carried out, and that he had already succeeded in a certain number of instances in producing immunity against the disease in animals. This announcement antedates by so much the announcements of Koch, and Grancher and Martin, that American medical men must feel an interest in maintaining the priority which belongs to this country.

In this particular matter it may be pointed out that Dr. Dixon in his announcement gives some indications as to the method by which he obtains the attenuated virus used in his experiments. Intimations of this sort are totally lacking in the communications of Koch, Grancher and Martin.

Literature Concerning the New Remedy for Tuberculosis.

[Editorial in THE AMERICAN NATURALIST, February, 1891.]

EDITORIAL.

Now that the first excitement regarding the new remedy for tuberculosis has subsided, the time seems opportune to glance back at the events of the past eighteen months, which have proved rich in scientific research in relation to the tubercle bacillus, and to place on record, not only for our own satisfaction, or even for those more immediately concerned, but especially for the benefit of succeeding generations, the announcements that have been made public from time to time in regard to that microbe, and the means that have been discovered for combating its ravages on the animal economy.

The endless and often embittered controversies which constantly occupy the literary world almost invariably arise from the fact that no plain contemporaneous record was made at the time, which would have placed the question beyond the range of argument. To cite a case in point—the circumstances surrounding the sale by Oliver Goldsmith of the "Vicar of Wake-

field" have proved an inexhaustible field for conjecture and surmise, and gallons of ink have been wasted over the attempts to reconcile two apparently conflicting accounts of that transaction.

In almost all cases of discovery there are rival claimants,—in some instances, where the evidence seemed most conflicting, it has been afterwards proved beyond question that the same idea has come to two workers, hundreds of miles apart, at almost identical moments. A little consideration will show that there is nothing very surprising in this. In the case of two scientific men pursuing an investigation on similar lines and with an identical goal in view, it is perfectly possible for them to hit upon the same conclusion at nearly the same time, and for both of them to believe that the one has been pillaging from the other.

In the case of the discovery of vaccination, no serious question ever arose, and Jenner stands out alone without challenge or dispute. The same can be said with regard to the discoveries of Pasteur, nor is there any doubt as to the claims of Professor Koch to the discovery of the tubercle bacillus.

In the month of March, 1882, Dr. Koch announced to the medical world that he had discovered the existence of a microbe hitherto unknown, and to which was given the name of the tubercle bacillus. He described how he had subjected diseased organs of numbers of men and animals to microscopic examination, and found, in all cases, the tubercles infested with a minute, rod-shaped parasite, which, by means of a special staining process, he differentiated from the surrounding tissue. He says: "It was in the highest degree impressive to observe in the center of the tubercle cell the minute organism which had created it."

Professor Klein differs from this view. He says: "I cannot agree with Koch, Watson Cheyne, and others, who maintain that each tubercle owes its origin to the immigration of the bacilli, for there is no difficulty in ascertaining that, in human tuberculosis, in tuberculosis of cattle, and in artificially induced tuberculosis of guinea-pigs and rabbits, there are met with tubercles in various stages, young and old, in which no trace of a bacillus is to be found, whereas, in the same section caseous tubercle may be present containing numbers of tubercle bacilli."

Transferring directly by inoculation the tuberculous matter from diseased animals to healthy ones he in every instance reproduced the disease. To meet the objection that it was not the parasite itself, but some virus in which it was embedded, he cultivated his bacilli artificially for long periods of time and through many successive generations.

This was confirmed by reliable investigations, and thus was established the existence of the tubercle bacillus and its discovery by him, and up to this time everything is plain sailing.

From the date of this announcement (1882) by Professor Koch up till October, 1889, nothing particularly new was heard on the subject, and as far as the literature on the tubercle bacillus goes, we have every reason to believe that the search for a toxic agent to combat the disease of tuberculosis and the ravages of the tubercle bacillus has been fruitless. Indeed, to all outside appearances, the tubercle bacillus, having been once discovered, was to be left unmolested to pursue its ravages on helpless humanity. But in reality it was being followed up by tireless and relentless foes.

On October 19th, 1889, was published

in the *Medical News*, of Philadelphia, by Dr. Samuel G. Dixon, at that time Professor of Hygiene to the University of Pennsylvania, a monograph announcing his discovery of the hitherto-unknown forms of the tubercle bacillus.

In the previous summer, whilst investigating different methods of technique and manipulation abroad, Dr. Dixon was led to believe that the bacillus could be cultivated so as to show lower forms of virulent life ; and following this idea up by a series of experiments, he was in a short time able to produce the hitherto-unnoticed forms of the bacilli, some club-shaped, others curved, and others again branched.

From the growths thus obtained, he proceeded to make a series of tube inoculations, from which he grew bacilli corresponding in every respect to the ordinary rod-shaped tubercle bacillus.

Having obtained these results, he propounded two hypotheses : 1st, That by a thorough filtering out of bacilli from tuberculous material a filtrate might be obtained and attenuated, so that by systematic inoculations a change might be produced in living animal tissues that would enable

them to resist virulent tubercle bacilli. 2d, To bring about a chemical change or physical change in living tissues that would resist tubercular phthisis, it is possible that inoculation with the bacillus would have to be made ; yet, before this could be done, the power of the virulent bacilli would have to be diminished, otherwise the result would be most disastrous. He added further that he had reduced the tubercle bacillus to a condition that, when inoculated into the animal economy, caused a resistance to the disease.

To use a military metaphor, this was the first note proclaiming that an active campaign had been opened on the tubercle bacillus, and specifying in terms as definite as possible the means by which the war was carried into the enemy's country.

The announcement of this discovery was widely circulated and commented upon, and reprints of the article were forwarded to Drs. Von Pettenkofer, Koch, Louder-Brunton, and other scientific investigators.

The International Medical Congress was appointed to meet in Berlin in August, 1890, and more than usual interest attached to its meeting, as it was generally rumored

that some important papers on the subject of the tubercle bacillus would be read on that occasion.

Nor was this rumor falsified, and the interest of he meeting may be said to have culminated as Professor Koch rose to address the assembled physicians, and when he stated that he had hit upon a substance which had the power of preventing the growth of the tubercle bacillus, it was greeted with loud applause. It was then stated that the bacillus of tuberculosis in man and chickens was very similar, and he inferred that the latter is a special species of the organic matter supposed to lie at the root of pulmonary consumption. He also announced that the direct action of solar light on the tubercle bacillus destroys in a certain length of time, varying from a few minutes to several hours, the virulence of this microbe.

It will be convenient to quote verbatim from that portion of the paper proclaiming his discovery of a toxic agent: "In spite of this failure—to effect any result on tuberculous animals with chemical substances—I have not allowed myself to be discouraged from prosecuting the search for growth-hindering remedies, and I have at

last hit upon a substance which has the power of preventing the growth of tubercle bacilli, not only in a test tube, but in the body of an animal. All experiments in tuberculosis are, as every one who has had experience of them has sufficiently discovered, of very long duration. My researches on this substance, therefore, although they have already occupied me for nearly a year, are not yet completed, and I can only say this much about them, that guinea-pigs, which, as is well known, are extraordinarily susceptible to tuberculosis, if exposed to the influence of this substance, cease to react to the inoculation of tuberculous virus, and that in guinea-pigs suffering from general tuberculosis, even to a high degree, the morbid process can be brought completely to a standstill without the body being in any way injuriously affected. From these researches I in the meantime do not draw any further conclusions than that the possibility of rendering pathogenic bacteria in the living body harmless without injury to the latter, which has hitherto been justly doubted has been thereby established." (Address before the Medical Congress in Berlin, August, 1890.)

It will be observed that Professor

Koch in his paper makes two points : 1st, The action of solar light and a high degree of heat in destroying the virulence of the microbe ; 2d, The fact that he had produced a substance the effect of which was to prevent the growth of the tubercle bacilli in the body of an animal, and that he produced a condition in the animal that was immune to the virulent tubercle bacilli ; also that he by the same process could overcome tuberculosis already established.

There are also two facts that cannot fail to strike the observer. The first is, that a period of over seven years had elapsed from the date of his first publication on the tubercle bacillus and that announcing his discovery of the toxic agent ; and the second, that his researches after the substance must have commenced about the period of Dr. Dixon's publication of October, 1889, of which, however, no mention is made in his address. It does not seem unfair to infer that Professor Koch had been unsuccessful during the preceding years in arriving at any satisfactory results. His own words, "My researches on this substance, therefore, although they have occupied me for nearly a year," etc., seems conclusive on this point. We do not, how-

ever, propose to do more than call attention to the coincidence of his researches after the toxic agent and the publication of Dr. Dixon's, October, 1889, the importance of which would be obvious to any bacteriologist, and the unfruitful nature of the former's investigations previous to that date.

There was, perhaps, a feeling prevalent in the medical world of incompleteness in the terms of Professor Koch's announcement, and it seems as if he had only stimulated curiosity in order to deny it satisfaction. Nor was this allayed when the news arrived from Berlin that the scientist, having brought his researches to a point sufficiently advanced to justify the use of his remedy *in corpore vili,* was prepared to inoculate the human subject. But the nature of his remedy and the method of its composition were to be kept a profound secret.

The first inoculation into the human economy took place on September 22d, in a case of lupus, but it was not until the first week in November that it was given out that Professor Koch was ready to make inoculations on a general scale. It is not germane, however, to our purpose to do

more than refer in passing to these events, or the exodus to Berlin, which is fresh in the public mind.

On November 15th Dr. Dixon, in the Philadelphia *Times and Register* (medical), clearly explained his position, as well as the result of his experiments up to that date. He wrote: "The hypotheses advanced in my terse article in the *Medical News* of October, 1889, have given the most brilliant results; yet I have never felt that the time had arrived for me to experiment on the human subject. Nor do I mean to be tempted to take any risks until the act would be purely an unselfish one. Even with the results that have been obtained in my laboratory, I would be sorry to have the general public stimulated with the idea that inoculation for tubercular phthisis had been perfected.

"Owing to the rumored report that Professor Koch has been, and is, inoculating human beings, it behooves me to await his results and understand his methods. If, however, it should appear that he is working on different lines, and that his plan is less dangerous than my own, it will be welcomed and adopted by me."

On November 18th Dr. Dixon laid

before the Academy of Natural Sciences a report summarizing in more detail his work of investigation on the tubercle bacillus. After alluding to the capability of the bacillus of changing from its commonly recognized rod-form to that of a more compound one, club-shaped, curved, or branched, which he believed to be either involution or degenerate forms, he went on to say: "There would appear to be in this homogeneous mass something other than the bodies of the micro-organisms. This may be the residue of the pabulum remaining after the bacilli have selected what was necessary for their existence, or a digestive secretion, or again it may be an excretion of the live organism. Let this be as it may, I hoped to find a changed functional action in the organism, in its secretion or excretion, that would combat tuberculosis in animal life, either by stimulating the cells or by causing a chemical reaction in the tissues that were susceptible to the digestive secretion of the tubercle bacillus.

"An attempt to explain its probable action appears in an article I wrote for the *Medical News* of October 19th, 1889, and also in the *Medical and Surgical Reporter*

and the *Times and Register* of this year. The views expressed are, however, purely hypothetical.

"When the mass that I have already spoken of as being found on the pabulum was subjected for a considerable length of time to various degrees of heat, and injected into the guinea-pig, the animal seemed to sicken, yet only for a short time. The animals so treated appear to resist injections of virulent bacilli. Whether this would produce immunity for any length of time, provided we discontinue the administration of the remedy, I am not sure. Some animals injected with the virulent matter after the treatment with the changed mass had been discontinued appear to be immune, and experiments on animals suffering with tuberculosis have resulted most satisfactorily."

It is evident from this report that Dr. Dixon had pushed his ideas advanced on October 19th, 1889, to a stage promising to confirm in a remarkable degree the hypotheses laid down in his monograph, and that inoculation by the toxic agent had yielded most satisfactory results.

It cannot fail also to be remarked that there is a definiteness of statement, as far

as the circumstances will admit, in Dr. Dixon's announcements which are lacking in those of his German colleague.

It soon became evident to Professor Koch that the attempt to withhold the composition of his remedy after it had been supplied to the profession was likely to defeat its own object. He therefore published on January 15th, 1891, a statement disclosing the nature of the remedy.

In this communication, after speaking of the preventive and curative effects of inoculating by living tubercle bacilli, he says : "This effect is not exclusively produced with living tubercular bacilli, but is also observed with the dead bacilli, the result being the same whether, as I discovered by experiments at the outset, the bacilli are killed by a somewhat prolonged application of a low temperature or boiling heat, or by means of certain chemicals. This peculiar fact I followed up in all directions, and this further result was obtained—that killed pure cultivations of tubercular bacilli, after rinsing in water, might be injected in great quantities under healthy guinea-pigs' skin without anything

occurring beyond local suppuration. If the injections are continued at intervals of from one to two days, the ulcerating inoculation wound becomes smaller and finally scars over, which otherwise it never does; the size of the swollen lymphatic glands is reduced, the body becomes better nourished, and the morbid process ceases, unless it has gone too far, in which case the animal perishes from exhaustion. By this means the basis of a curative process against tuberculosis was established."

We have underlined these words in order to call the reader's attention in connection with their identical nature with the following statement by Dr. Dixon, published months before: "That by submitting a mass of growing bacilli to different degrees of heat, etc., and injecting the mass into animals, he not only prevented tuberculosis, but also cured the same."

Compare this with Koch's just published claim, that by injecting tubercle bacilli that had been submitted to solar light, heat, etc., he had produced in guinea-pigs immunity, and also cure, and moreover that by this the curative process against tuberculosis was established, and if there is any difference between the two, we have not been able to detect it.

With this last utterance of Professor Koch the literature on the subject of the cure for tuberculosis for the present ceases.

We have endeavored to lay before our readers a succinct and chronological account of the history of this great discovery.

The important question as to whom belongs the credit for it, and to whom should be awarded the priority, may well be left to them. We venture to think that the material is present here before them to enable them to form a correct judgment.

That the use of the remedy has not yielded the results expected from it by Professor Koch is very probable, and it is difficult to avoid the reflection that a more conservative policy, such as that persistently advocated and followed by Dr. Dixon, would have been wiser, and moreover kinder to those whose hope of cure had been unduly raised. There is abundant work to be done yet in the laboratories before definite conclusions can be reached, and the inoculation into the human system is therefore to be deprecated as premature. That the main principle has been arrived at seems beyond doubt, but much yet remains before the discovery can become of permanent benefit to suffering humanity.

The Present Status of the New Treatment of Tuberculosis.

[Editoral from THE MEDICAL AND SURGICAL REPORTER, May 9, 1891.]

THE PRESENT STATUS OF THE NEW TREATMENT OF TUBERCULOSIS.

The absence of exact science in the medical knowledge of the day, has perhaps been nowhere so well exemplified as in the extreme readiness of both profession and laity to accept the unproved word of a single man in relation to a hitherto unanswered and weighty question in therapeutics—that of the existence of a specific control of the tubercular process. Nor is the precipitate haste on the part of the clinicians to condemn the method, as yet not even half tried, any more evidence of the development of stable principles in our methods of combatting disease processes. From a theoretical standpoint, excluding from present consideration the general care and management of the patient, the destruction, or modification of the *materies morbi* is to be accomplished in four probable ways, these include: the utilization of the antagonism of micro-organisms toward each other; the deleterious effect of micro-organismal products on the growth of micro-

organisms ; the unfavorable effects on micro-organisms of certain agents of mineral or organic origin ; and the production of general surroundings unfavorable to the advance of the infection, both in the individual and in the community. To the second of these groups is to be referred the method recently proposed by Prof. Koch for combating the tubercular process. This method, which is substantially if not precisely identical with the measures previously employed and announced by Dixon of this city, has for its underlying principle a fact, the verity of which may easily be recognized by analogy in numerous instances of the incompatibility of waste products with productive growths. Thus alcohol, as a product of vegetable activity manifested as fermentation, when present in proportions beyond 20 per cent., is sufficient to retard and eventually destroy the actions and vitality of the ferment. Nor is the use of the products of bacteria as a means of altering the further growth of bacteria in the animal tissues by any means a recent one, as may be noted in relation to the work done upon the bacillus pyocyaneus by Charrin and others. Separation of the fluid product of the growth of this last bacterium from the culture itself, by means of an

unglazed porcelain filter, and inoculation with this sterile product has prevented the inception of pyocyanic disease in animals after subsequent inoculations with virulent matter. Probably the same principle underlies the Pasteur method of hydrophobic prevention ; and the field of preventive medicine glows with promise of great and near discoveries in this same line in other diseases.

The substance used by Koch in his experiments and more recently in the treatment of tuberculosis in man, and which as already stated, is produced in practically the same manner by Dixon, is obtained from cultures of tubercle bacilli exposed to altered conditious of life by means of extraction with some such menstruum as glycerine. This material, from which no definite active agent has been eliminated by Koch, when brought into contact with tubercular growth in the animal economy, is announced to produce decided lowering of activity of growth, and eventually, if in sufficient proportion, to permanently stop the morbid process. In the animal economy, further, as an evidence of its action, whether by direct action upon the germ, or by inducing deleterious changes in the tubercular tissues, there is manifested a febrile

re-action ; and as a result of its action it is stated that there is a destruction of the diseased structures and subsequently their replacement by cicatricial tissue. The exact mode of operation is not known, various theories having been offered in explanation.

Such was the knowledge established by the researches of Dixon and Koch, and eagerly seized upon by the entire world in the expectation of mastering tuberculosis. In the natural course of the rapid popularization of so important a discovery, the limits of its application have been wittingly as well as ignorantly widely overstepped ; badly diagnosed cases and cases whose only cure can be death, have been subjected to the vicissitudes of the treatment. With an eye singly to the result of the means upon the tuberculosis, cases have been permitted to approach the fatal termination because of the neglect of the true end, the recovery of the patient ; and too often even the increased nutritive need of the weakened system has been passed by in the endeavor to overcome the process at fault. Clearly, in the method of action of the substance it was to be recognized that its only safe application could be found in the most localized forms, and preferably in foci

where elimination of the products could be performed most thoroughly and with least severity to the organism ; nevertheless, in the mad hurry, cases of advanced degrees of the disease and cases marked by generalization of the malady have been permitted the treatment, only to swell the death list which has been heaping discredit upon the measure. Where tubercular foci are numerous and widely distributed, if each focus is to be the scene ot rapid necrotic processes, each followed by a local focus of reactive inflammation, what is to be expected but the effects of an intense toxæmia and fever, which are the necessary attendants of such a condition ?

Where the lungs are riddled with the tubercular changes of late chronic phthisis, what is to be expected if this new therapeutic agent accomplish the best possible results, and yet leave a great mass of cicatricial results to block up and hamper the pulmonary tissue ? Moreover, what of that great mass of patients, from whom, the treatment having failed to produce notable external changes, the lymph was withdrawn and death followed—are there positive evidences of no palpable changes in the internal tubercular localities in the line of change indicated ? How is it possible

from post-mortem appearances to affirm absolutely the generalization of the tubercular process in this or that position, within a definite and brief period? These are the considerations upon which more information and more definite knowledge should be demanded from those who condemn the method. Its action upon the true cases of lupus has been too decisive to permit, in other localized forms of tuberculosis, any discredit until more exact information is had. The conflict of reports is too great at the present date and the tendency of medical opinion too observant of so-called policy to allow an absolute decision; this will and can only come when the lymph method has fallen entirely out of injudicious hands and is left to the investigation of the cautious and thoroughly interested.

There are other phases of this subject, too, which cannot fail to attract attention in the future. How much of the severity of the reactions, and how much the failure in results may be due to the presence of substances other than the essential toxalbumen in the lymph? What auxiliary measures are those best adapted to the furtherance of the favorable results of treatment? Finally, if even in mild cases

of pulmonary tuberculosis failure should be established, there is one other point of the utmost importance to be examined. In the earliest paper of Dixon (Med. News, Nov., '89), antedating Koch's announcement by more than a year, there were distinct expressions of the development of immunity in animal tissues against the tubercular process by this general method ; and investigations carried on in rabbits and guinea-pigs have with considerable uniformity confirmed this hypothesis. It is undoubtedly an injudicious act to inoculate healthy individuals with an agent of which so little is known as this mixture of the retrograde products of tubercle bacilli, but it has been and doubtless will be done more or less frequently for a time. There are no positive arguments in relation to tuberculosis refuting the usual rule of infections to protect against themselves ; and there do occur occasional cases whose clinical histories present features not averse to this view. For example, within the knowledge of the writer, a young man of questionable family history, who for 20 years had had a destructive scrofuloderm only cured within the past few years, became accidently inoculated with tuberculosis, while performing an autopsy upon a tubercular body. To ordinary observation, the usual course of inoculated tuberculosis was manifested, the healing of the original wound, the period of some days' quiescence, the formation of a nodule at the site of sore, and the breaking down of the surface into a slightly

purulent fluid to the formation of a tubercular ulcer. Within more than a month no lymphatic involvement had become manifest, and the local node was removed by operation. Thus far, nearly five months, there is no evidence of general infection. Such cases have occurred before, and the process remained for a long time localized —yet may not the previous tubercular condition as manifested by the existence of scrofula, have exerted some limiting influence upon the inoculated process? The existence in otherwise normal lungs of isolated and calcified nodes of old tubercular processes may suggest the protective value of the results of the prior disease; and where these are associated with evidences of general advancement of the process there enters the question of whether there had not been at least a temporary protection analogous to that afforded by vaccination.

This then is the status of the proposition. The statements denying value to the treatment of tuberculosis by the method of Koch, whose claim to consideration rests upon what appear to be general laws, and is corroborated by laboratory researches, lose their own force from the numerous faults of omission and commission met in the widespread and ignorant application of the method. Even should it fail as a curative, except in the localized and superficial variety known as lupus, there is yet another field for its usefulness open to investigation, its positive preventive power.

[Editorial in THE REVIEW OF INSANITY AND NERVOUS DISEASES, U. S. A., June, 1891.]

In the wild enthusiasm over Koch's discovery it has been apparently forgotten that Dr. Sam'l G. Dixon, of Philadelphia, practically anticipated Koch by a year in his method of treating tuberculosis. Dr. Dixon's discovery was announced in the *Medical News*, in 1889, and his remedy and that of Koch is essentially the same. Though experience has not sustained the expectations held concerning the remedy, we yet believe it to be a great discovery. It at least indicates the probability of a remedy for bacterial diseases and points the way for future investigations. We believe a remedy for these diseases will some day be found, and when that is done, Dixon and Koch will be regarded as having been the first to demonstrate the possibility of such a thing. We call attention to this matter now. chiefly for the purpose of emphasizing Dr. Dixon's prior discovery. While American physicians are screaming themselves hoarse over Dr. Koch, we trust they also uncover to their modest fellow countryman, who antedated the great German's discovery by at least a year.

Date Due