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ORIGINAL ARTICLES.

ON THE DEVELOPMENT OF THE CAUSAL TREATMENT OF TUBERCULOSIS.

BY EDWIN KLEBS, M.D.

CHICAGO, ILL.

I will not state in this paper the whole history of this question, which at its first commencement excited so much enthusiasm, and later caused so much disappointment to all concerned. As one of the few observers, having published detailed reports on the question ("On the Causal Treatment of Tuberculosis," Hamburg-Leipzig, 1894), I may be justified in expressing my regret that so many of the works on this subject, mostly in Germany, are written in the obscure and abbreviated style possibly appropriate for "vorläufige Mittheilungen," but not for definite scientific work.

Robert Koch, in his first paper on "Tuberculin" (1890), showed the effects of this substance on tuberculous rabbits, but never gave later detailed accounts of his experiments. Everyone wishing to work on the subject was therefore obliged to find his way in the dark. Indeed, the preparation of tuberculin was not published for a long time afterward. Finding that the often dangerous effect of tuberculin shown by Virchow, Hansemann and others was effected by toxins, I tried to eliminate those substances which I found unnecessary for the undoubted healing effect sometimes observed in tuberculin treatment. While Koch would avoid the faults of his first treatment by giving very small doses of tuberculin, his pupil, Dr. Carl Spengler of Davos, declares that small doses are not efficient. He also finds that the feverish reaction after the injection will not be necessary for the healing process. He says, in his pamphlet ("Ueber Tuberculin Behandlung," Davos, 1897, p. 7), "the small doses recommended before oftentimes may bring some relief to some phthisics, but for definite healing they are not sufficient. On tuberculous infected animals which should die in eleven weeks, the small doses do not work at all." The last is a valuable confirmation of the efficiency of the tuberculin for healing purposes, this sort of infection being very slight if guinea-pigs are used.

These results of practical experience, emphasized in 1897, are exactly the same proclaimed by me in 1894 as the results of experimental and clinical work. If now Dr. Spengler has not words for stating this fact, he can not be excused on the ground of ignorance, as I conferred with him at length, before he migrated to the camp of Dr. Koch. He may be excused, as he follows the method of his master, and we shall see that the latter is responsible for the suppression of facts, as yet not known in the German scientific world. The latest publication of Dr. Koch, in the *Deutsche Medicinische Wochenschrift*, April 1, 1897, has provoked the very justified reclamation of

Dr. Hans Buchner in Munich and his brother in Tübingen, regarding the preparation of his new tuberculin, the so-called TR. It has always been the custom in Germany, and I think in all civilized countries, to name the author of a method that one uses for a similar purpose. This conceded, we must ask if the Buchner method to procure the products of living bacteria by mechanical destruction of the cells can give substances more efficient for medical purpose, than the simple extracts made by watery or glycerin solutions of salt, acting on the killed bacilli? That will depend mostly on the agencies used for the destruction of life. I am very glad to hear, from Koch and Spengler, that they accepted my view that the cooking of tubercle cultures destroys a good deal of the healing substances. The substituted concentration *in vacuo*, for many years practiced in my laboratory, is the principle set forth in my book.

Spengler asserts that this new tuberculin of Koch, named TO (original "Tuberculin after Spengler" a somewhat curious expression for an improved tuberculin), gives higher febrile reactions than the former preparation. In consequence of the extreme danger connected with the use of such toxic products, it must be excluded from therapeutic use.

As I have shown in my book (1894), the action of the tuberculo-toxins lies in two directions, first in a depression of the heart action, shown by kymographic experiments on dogs and rabbits, animals much more resistant to the tubercular infection than men and guinea-pigs. I could also observe this same highly dangerous influence in tubercular patients, at first supporting the tuberculin treatment, but after some time showing very grave convulsions, probably effected by the impaired action of the heart. Further experiments on animals have shown me that these toxins have a highly cumulative action, probably due to the slow secretion of these substances. White rats, which are very resistant to tuberculosis, can be killed by this agent in thirty to fifty minutes under convulsions and cyanosis. I must emphatically declare that the TO must be rejected totally as a therapeutic agent.

The second deleterious action of these tuberculo-toxins is the local necrosis of the tuberculous parts, once held by Koch as the true healing action of his remedy. I have shown in my book that the tubercle bacilli develop rapidly in necrotic tissue, and have explained from this observation the rapid dissemination of tuberculosis after the tuberculin treatment. Regarding the cases observed in the pathologic institution of Virchow (1890 to 1891), it is difficult to understand how Spengler can suggest, in 1897, that these cases can be explained as a commencement of miliary tuberculosis preceding the injections. If he will reread the lecture on these observations, he will find cases in which the disease, before the treatment, never had a febrile character.

On this account I rejected the tuberculin treatment

and experimented to make the treatment innocuous by chemic elimination of the toxins. The tuberculocidin was the result of these researches, published in detail in my book. I stated that this substance not only killed living tubercle bacilli in the test-tube, but healed far advanced tuberculosis in guinea-pigs. In five years, hundreds of cases of human tuberculosis have been treated with very good results, in Europe and in this country. A milder acting form was the antiphthisin, which contains only substances taken from the fluid of the cultures—as I believe, mostly secretion products of the bacilli, toxic for its productions, but not for the human body. The good results of AP in very irritable forms of tuberculosis have been obvious; the killing power was demonstrated by experiments made in Asheville, N. C. (Winah Sanitarium). With these two products of tubercle culture we had very good results, as reported in this country by a vast number of most reliable physicians, using more than 50 liters the last year.

I undertook during the last two years renewed experiments on the question of immunization in tuberculosis. In 1876 I had found some indications in my experimental work, that even in tuberculosis this property was not absent. New proofs were brought forth in my book (1894), but sharply criticised by one of my severest critics, Dr. Lubarsch, formerly my assistant in Zurich. As Dr. Lubarsch has himself worked on immunization, his criticism may have made some impression.

Later I published my experiences made in this country on this question (JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, July 25, 1896; *Centralblatt für Bacteriologie*, Nos. 14 and 15, 1896), and am satisfied that Dr. Koch built up his new theory on the same principle, but, curiously, not remembering my work. As to the clinical support of this view, we may say that the long period of latency of the disease, as well as the results of causal treatment, accord fully in this direction. Koch is now searching for immunizing substances in the tubercle bacilli, as I did before. His TR, the crushed substance of dry living tubercle bacilli, will have this power of immunization. How much must be given in proportion to the weight of the patient, or the quantity of immunizing or only organic matter contained in his TR, is not noted in his communication. In some of his animal test cases the immunization is not finished, in others perfect. We would be very grateful to hear the history of these experimental cases. Without that the proof is not so positive. The responsibility of the physicians will be sustained alone by the reputation of the author, not disputable in all bacterial, but somewhat doubtful in therapeutic questions, as shown by the tuberculin treatment.

The manner of preparation of the TR involves some questions that should be answered before the treatment with this substance could safely commence. Living virulent bacilli are crushed mechanically so long as no tubercle bacilli can be detected in the obtained fluid. The rest of the indissoluble substance should be very small, and the fluid perfectly clear or opalescent. The addition of 10 per cent. glycerin should be sufficient for conservation.

1. If living tubercle bacilli are crushed and extracted, it is to be feared that some of them will remain. That they can be wholly eliminated by the use of centrifuge is doubtful, as the fluid is by no means a true solution, but a gelatinous soaked-up mass. The precipitation

by addition of glycerin, more than 10 per cent., noted by Koch, shows this clearly. In such a substance particles not much different in specific weight will not follow the centrifugal motion. Indeed, this substance contains, according to Koch, masses stainable by methylene-blue, consisting mostly of the bodies of tubercle bacilli freed from their fatty contents during the experiments. Are these bacilli, deprived of their fat, living or not? We do not know that and have no other means for deciding this question than the animal experiment, the infection. I have some reason for suggesting that in the living animal and in men tubercle bacilli are also present, which do not stain acid-proof with fuchsin, but stain after the method of Gram. The question arises whether the new TR will be tested in every animal experiment as to whether it is infectious or not?

2. For conservation of this fluid Koch adds to the crushed and centrifuged preparation 10 per cent. glycerin. But it is generally accepted that organisms grow very well in such a fluid. This is the more to be regarded as the manner of preparation does not guarantee the aseptic condition. The way of avoiding this difficulty should be published.

Experiments can only decide these questions, and they should be reported in a detailed manner. In these complicated experiments, in which the variability of animal life accords with the variability of microbic life and only one factor, the chemical product, can be made constant, without a greater number of scientifically varied experiments nothing can be decided. The whole material must be published, so that any one can judge from the evidence.

3. Lastly, we come to the comparison of the two existing methods for preparing immunizing and healing substances from the cultures of tubercle bacilli, the tuberculocidin and TR. Koch remarks in his last publication that the presence of fat in these organisms, which gives the substance the specific reaction, as shown first by me, hindered the extraction of tubercle bacilli. That this is not true is shown by experiments by the director of my laboratory in Strassburg, Dr. Ernest Klebs, who gives the following account:

ANALYTICAL DETERMINATION OF THE EXTRACT OF TUBERCLE CULTURES.

"Of five liters tubercle cultures exactly four weeks old and grown perfectly, I made the determination of organic substances in the fluid. The cultures after they were taken out of the incubator were first killed by ortho-kresol, then mixed and preserved in a room of normal temperature (January and February). The results of the analysis were as follows. (The glycerin was extracted in the platinum-crucible with ether and alcohol, 3 to 1, before drying the residue.)

1.	Extract 24 hours after killing the T. B.,	1.64 per cent.
2.	" 7 days " " "	1.71 "
3.	" 14 " " " "	1.86 "
4.	" 21 " " " "	1.88 "
5.	" 35 " " " "	2.20 "
6.	" 42 " " " "	2.44 "

The difference between analysis No. 6 and No. 1 is: $2.44 - 1.64 = 0.8$ per cent. In six weeks in the liter of the cultures nearly eight grams more are gone in solution. That result is very remarkable, but I found nearly the same quantity, 7.9 per cent., last summer, as I wrote you."

In this last experiment the strongest toxin I ever received was obtained by concentrating *in vacuo*. Tuberculous guinea-pigs of 700 grams weight are

killed by 0.3 gram weight in less than twenty-four hours and 0.5 c.c. kills sound white rats of 150 grams weight in thirty to fifty minutes. It seems to be identical with the TO of R. Koch. After this result I can not think that by any method more soluble substance can be extracted from the tuberculin bacilli by a fluid containing 5 per cent. glycerin. The high toxic effect of this substance is defending the use for healing purposes, which view Koch seems also to accept by going over to the production of TR. All these extracted substances are contained in the tuberculocidin (TC), eliminating the toxins by precipitation with sodium bismuth iodid. The often repeated effect of this substance is that the higher temperature of tuberculous animals and man is suppressed and the tubercle bacilli are killed, the tuberculous tissue reabsorbed without formation of scars where the tissues are not wholly necrotized. That also the gravest infection of guinea-pigs can heal I have shown last year. (JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, l. c.) It seems to me to be of the highest value to compare the immunizing property of the tubercle bacilli extract made without crushing the T.B. and after crushing them as is made in the preparation of TR. In experiments on guinea-pigs, begun immediately after having received the publication of Koch (in April) on T. B. killed with kresol, 0.2 per cent., I have found no difference in the immunizing power of the extracts made by my method and by the method of Koch. The first seemed to be more efficient, but this may depend on a somewhat higher concentration. So I am sure that the precipitation with NaBiI₂ does not destroy the immunizing substance contained in the T. B. As to the question, whether living T. B. give more of this substance, it seems to me very questionable, for if this substance would be destroyed by the death of T. B. our preparations must have become totally ineffectual.

The difficulties in preparing TR from living T. B. lie, as I have shown, in the danger of the presence of some living T. B. in the fluid as long as the fluid is opalescent, by the presence of gelatinous matter. Within the last few days I have found a method of eliminating these certainly superfluous or dangerous admixtures, using the usual centrifuge, giving no more than 2,680 rotations per minute. By adding finely powdered carbonate of magnesia the fluid can be cleared up by a rotation of 2,000 per minute. All this gelatinous matter and with it some T. B. escaping the crushing is precipitated and included in the magnesia deposit. The experiments with these fluids will be begun now and will be referred to in due time. Addition of conservative fluids, as 0.2 per cent. orthocresol, will be tried in these experiments. The danger of contamination at the time of the preparation must be avoided, as far as possible, by always using fluids immediately after having centrifuged them with magnesia-carbonate. For human use such preparations must be avoided, but the theoretic question seems to be interesting.

Wire Springs to Hold open Operated Abscesses.—E. Braatz uses a small wire spring shaped something like a fancy W, or a spiral for deep abscesses, to keep the openings from closing after evacuation of the pus, thus facilitating free discharge. He has them made in various sizes, and if necessary, combines a rubber drain with them, which he always slits lengthwise, to secure better drainage. This is a return to the old spirals of Chassaignac.—*Cbl. f. Chir.*, April 24.

GENERAL MEDICINE A SPECIALTY IN ITSELF; ITS RELATION TO THE RECOGNIZED SPECIALTIES, PARTICULARLY TO BACTERIOLOGY.

Read in the Section on Practice of Medicine, at the Forty-eighth Annual Meeting of the American Medical Association, at Philadelphia, Pa., June 1-4, 1897.

BY GEORGE BYRD HARRISON, M.D.

President of the Obstetrical, Gynecological and Pediatric Society; Professor of Diseases of Children, Columbian University; Senior Physician Washington City Orphan Asylum; Member of Attending Staff, Department of General Diseases Central Dispensary and Emergency Hospital, etc.
WASHINGTON, D. C.

I wish to urge upon you, as forcibly as I can, that the time has come when we should claim with all our energy that the department of medicine in which we are engaged (the noblest of all the divisions of the science, because the most comprehensive, and calling into play the intellectual faculties as none other can possibly do), is, and of right should be, a *specialty* in itself, claiming not only *recognition* from the "manipulative" (or otherwise limited), recognized specialties, but occupying toward them the position of a parent to children—a fostering care which they can not do without, unless they are content to be relegated to the domain of sciolism and quackery. These are strong expressions, but not too emphatic for the occasion. A brilliant medical man, of admirable attainment in the theory of medicine, of thorough hospital training and very considerable experience in private practice, told me (within a few weeks), that he had made up his mind to quit private practice and enter the Marine-Hospital Service. Having been out of the class-room so long, and with little time to prepare for examination, he had some misgivings as to his ability to compete with men fresh from their textbooks. But, he added, I have come to this deliberate conclusion, that the time is not far distant when none but the rich can afford to indulge in the practice of general medicine. He carried out his plan, and out of three places competed for by thirty odd applicants, took the first position and is now installed in that service. This illustration of what is likely to occur very generally, has struck me forcibly. If the present system goes on we will all be impelled to *quasi* specialism—which is as dishonest as modern homeopathy—or else to give up civil practice altogether.

Let us contemplate the picture as it is presented day by day. We call a laryngologist to a case, because under the Hippocratic oath we feel obliged to give the patient the advantage of manipulative skill and constant practice. Everything goes well with this individual, and we congratulate ourselves upon our consideration for the patient and his friends. Very soon we hear of another case in the same household, construed by the friends to be a suitable one for a specialist, and the specialist whom we have introduced is installed. Perhaps there may have been a shade of difference in the conditions, and with our superior knowledge of the qualifications of the various men engaged in this line, we might have preferred some one else to meet the phenomena which long acquaintance with the patient and his relations makes us more fit to interpret than any one else; but the man whom we introduced into the household takes not only precedence, but absolute *control* of the situation; we have not even an opportunity for remonstrance, much less of interference.