A CONTRIBUTION TO THE ÆTIOLOGICAL TREATMENT OF TUBERCULOSIS.

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THE classical investigations of Edward Jenner in the prevention of small-pox led the way to successful treatment of other infectious diseases. Marked advance has been made during the last fifteen years. It is natural that much attention should have been given to the prophylaxis and treatment of so widespread and dangerous a disease as tuberculosis. The first experiments in this direction were made by the distinguished discoverer of the tubercle bacilli, Robert Koch, as far back as 1890. At the Tenth International Medical Congress in Berlin, in the above-mentioned year, Koch announced that after long researches he had found a substance which, not only in the laboratory, but also within the tissues of the living organism, hindered the growth of the tubercle bacillus. After this announcement many investigators followed in the footsteps of Koch. Eager search has been made for some satisfactory means whereby active as well as passive immunity might be procured.

It is unnecessary to refer in detail to the numerous experiments dealing with this subject. I will only briefly mention that Koch, after the introduction of his old tuberculin, has brought forward a new tuberculin (T.R.). The first contrives to be used mainly for diagnostic purposes, while the second is chiefly employed as a curative agent. I myself have used Koch's new tuberculin in eighty-seven different cases.

Koch has prepared his tuberculin from the organisms of human tuberculosis; Roux has made a tuberculin from the bacilli of avian tuberculosis; and Ramont and Ravant have introduced a so-called fish-tuberculin. Klebs introduced his tuberculocidin in 1891, and this is still to be obtained. Alfred Thamm has brought forward a tuberculo-albumin, Landman "tuberculol," Hirschfelder an "oxytuberculin," and Spengler a combination of tuberculin and tuberculocidin.

Substances similar to Koch's new tuberculin have been described by several experimenters; Buchner and Hahn, for instance, have made what they term "tuberculo-plasmin." Other experimenters have used for the preparation of immunizing bodies tubercle bacilli from other than human sources; McFadyean, for instance, has used avian tubercle;

Terre, fish tubercle ; Dieudonné, frog tubercle ; and Friedmann, turtle tubercle.

Von Behring has immunized cattle with the products of living human tubercle bacilli ("bovovaccin"), and has proposed that the milk of such immunized cows should be used for the nourishment of children. Von Baumgarten has also made calves immune, by means of a human tuberculin, against invasion by bovine tubercle. Koch and Klemperer have worked in the same direction, and the recent experiments of Calmette should be mentioned. Von Behring has introduced a substance called "tulase," recommending it for immunization of human beings against tuberculosis, and von Ruck has experimented in much the same way.

Besides the above-mentioned endeavours to produce active immunity, attempts have been made to secure good results by means of a passive immunity. The first experiments in this direction were made by E. Maragliano in 1895. Sera have also been introduced by Richet, Hericourt, and Babes.

A. Marmorek has recommended a special anti-tuberculosis serum which has been used to some extent. I myself have used it in thirty-five cases, but without any encouraging results. Among others, Trudeau, Baldwin, Auclair, De Schweinitz, Prioleau, Paquin, Redou, Chenot, Ferran, Dörrenberg, and Broca have also endeavoured to discover satisfactory means for the establishment of an immunization against tuberculosis.

Progress has been made by the production of an active rather than a passive immunization. It seems very probable that the final solution of the problem will be found in this direction. We can regard it as nearly certain that the treatment of tuberculosis by vaccines or sera will before long be well established.

What is the best means to secure this active immunization is still under discussion. Many hold that immunization substances which contain the organisms themselves more or less changed, and not only their toxins, are the less dangerous, and give more hope of good results.

Here arises the question as to the means which should be adopted to render the tubercle bacilli so enfeebled that, while their immunization matters do not disappear, dangerous substances shall be got rid of.

From this point of view I have experimented a long time. Finally I have succeeded, by the use of different lights and chemical materials, in obtaining a substance from the pure culture of the human tubercle bacilli which seems to be not at all dangerous, and which also undoubtedly exerts healing properties. This substance I have called "tubos." That it is not at all dangerous I have proved by elaborate

experiments on guinea-pigs, animals which, as is well known, are peculiarly sensitive to tuberculosis infection. I injected comparatively large doses of "tubos" into young guinea-pigs, and then followed the development of them at the same time as that of the development of the young of the non-injected control-animal. The young of the injected animals develop well, and with the same celerity as the young of the non-injected animals. This fact, it seems to me, shows that "tubos" is not dangerous for guinea-pigs. These experiments have been repeated with similar results in rabbits.

In experiments on animals this material, "tubos," when injected, either before or after inoculation with tubercle bacilli, has shown in a remarkable degree a hindering influence to the development of tuberculous lesions.

The guinea-pigs injected with "tubos" have died, on the average, within eighty-four days; some, indeed, have survived the infection, while again the control-animals died, on the average, within forty-one days. It is not easy, as is known, to measure the quantity of tubercle bacilli which is enough to kill the animals in question. It is possible that I have injected much more than the simple lethal dose of the tubercle bacilli in these experiments, and one cannot quite accurately estimate the preventive power of "tubos," although a remarkable preventive influence can, without doubt, be observed. At the present time I am engaged in researches regarding the exact lethal dose of the tubercle bacilli, and how best such may be measured.

I have shown by my experiments that "tubos" was not dangerous, but had a preventive and curative influence. I extended my investigations to the human tuberculous subject, taking cases of pulmonary consumption and other tuberculous diseases. But to be quite sure that the material was not dangerous for the human body, I have injected the material subcutaneously three times in the week during two months into myself, and have tried to observe if anything prejudicial occurred—weight, working capacity, appetite, sleep, temperature, all remained normal, and no pain or other troubles were remarked. I then began to use "tubos" carefully, although in much smaller doses than I had used on myself. I first employed it for the treatment of consumptive patients in my own private hospital, Lepokoti Tiikka (fifty beds), in the near neighbourhood of Helsingfors. For the most part only such cases as were far developed (those where the consumption was in both lungs and sometimes in the throat) were treated with "tubos" injections.

Up to the present time fifty cases have been treated. The treatment has been completed in about thirty cases, or the patients are now under observation.

From these fifty cases one can estimate that 26·7 per cent. are

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"cured" or "arrested," while 46·9 per cent. appeared improved, and 18·3 per cent. remained unchanged. Most of these, it must be remembered, have been treated only for a very short time; the rest have become worse or have died. Among the "cured" cases was that of a young woman who had tuberculous peritonitis.

I have used "tubos" in emulsion 1 : 1000 of the dry substance. The injection doses are as follows :

For the guinea-pigs,	0·001	dry substance ; it is 1 cm. ³ of the emulsion.
For the rabbits, also the same	...	... 0·001 dry substance.
For myself	...	... 0·0004 "
For human patients in the beginning...	...	... 0·0002 "
For human patients later	...	... 0·0003 "

The injection was always used subcutaneously, and did not cause boils. If the injection has been made in the back as usual, no swelling or other irritation has been observed, and only very seldom a little pain on the injected place, so that the material seems to have been well absorbed. But if I injected in the arms or lower part of the legs, a little, hard and painful swelling has sometimes been observed, which has, however, disappeared within a few days. No great pain nor rise in temperature has been observed. In many cases, on the contrary, the temperature has become lower after the injection.

I must also add that during the treatment with "tubos" the patient has been subjected to rigid dietetical management as well as open-air treatment. But even allowing for the action of these remedial factors, I consider the results with "tubos" to have been very encouraging.

I well understand that an experiment with such a new substance is very difficult, and results may easily mislead. It is quite clear to my own mind that the experiments here referred to, and the results obtained, are all too small to allow us to draw any certain conclusions. They, however, seem to justify, and even demand, further investigation.