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The Hidden History of Tuberculin

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1. Introduction

Robert Koch was an eminence on Tuberculosis and a German hero worldwide since he discovered and described the etiologic cause of the white plague. Soon afterwards, he devoted his work to study the effect of inoculating *M.tuberculosis* bacilli (Mtb) to guinea pigs, either healthy or already infected. From his experiments, as reported by himself, he learnt the infection was able to develop protection against reinfection in some extent and that using small doses of dead bacilli could help to heal the tuberculous lesions in the infected animals, while large doses could kill them. The 4th of July, 1890, during the International Medical Congress in Berlin, he announced he might have found a cure, and pointed out it should not be used in severe cases as it could do more harm than good. However, tuberculosis was one of the main causes of death at that moment, and the word of Koch's finding its cure rapidly spread. Many physicians from all over the world traveled to Berlin to learn how to use the new remedy, called tuberculin for being obtained from Mtb bacilli, as Sir Conan Doyle did himself. Koch, probably scared of the great expectancy generated by his cure still not too well-known, decided to write a manuscript entitled "A further report on a remedy for tuberculosis" (Koch 1890), which was published on mid-November of the same year. With this paper, he intended to clarify and to give a review of the subject, in order to avoid the public to get distorted knowledge on the remedy proposed by him. In the manuscript, he tried to explain why tuberculin worked: he believed the treatment was able to destroy the necrotic tissue of the tuberculous lesions, and this was the cause for the bacilli to die subsequently. But still more important, he cautioned about the fact of existing reactions following the inoculation of tuberculin, which severity depended on the patients and their previous illness status, and suggested it should be applied as early as possible to obtain a positive outcome (Koch 1890).

2. Tuberculins

2.1 Koch's tuberculin

Tuberculin was fine powder of Mtb (obtained after mechanically comminuting the products from a tubercle culture) brought into suspension, used in dilutions and sterilised by heating it. It was injected subcutaneously in the back, between the shoulder-blades and the lumbar region, for being the location where less local reactions (including pain) were recorded (Koch 1890). High doses were given in a schedule based in the inoculation of increasing doses. The

inoculation of tuberculin was followed by the so-called „Reactions“, which in some cases were large and quite severe, sometimes leading to death.

There were three types of reactions depending on where did they happen: local, general (which we nowadays would call systemic) or focal reactions (in tuberculous lesions)(Riviere and Morland 1913).

At the injection site, if existing, the local reactions included redness, inflammatory swelling and pain, signs and symptoms which used to appear 2 or 3 days after the inoculation, were well-tolerated and tended to disappear. Fever was the more constant sign among the general reactions, followed by headache, malaise, lost of appetite and nausea. The amount of fever varied among the individuals, and didn't previewed any outcome, neither good or bad (Ross 19--?).

Focal reactions included haemoptysis, pleuritic pain, greater cough, râles and swelling of lymphatic glands. These were the most feared reactions but also the most wanted ones, as giving T was endeavoured to help to solve the tuberculous lesions. People well-reacting to the treatment reached, in a period in between 8 weeks and 4 months, a cessation of sweating, cough and expectoration, an improvement of the general condition and a clearing up of the moist rales, which meant the necrotic and ulcerating lesion to become cicatricial (Ross 19--?).

But due to the sudden and massive use of Koch's new remedy, lots of cases with negative outcome reached the mass media as well as the scientific community.

Only one year after presenting T, Koch himself commented the reactions observed by other physicians when using it (Pottenger 1913).

In spite of the recommendations of Koch's to carefully select the patients to be treated, tuberculin was given to any patient, including greatly advanced cases of tuberculosis, with large cavities. While some physicians praised for the benefits on some clinical forms of tuberculosis, specially when combined to surgery (tuberculosis of joints, bones and lupus) (Ross 19--?; Anonymous 1891; Morris 1893), many deaths were also reported. Due to them, and to the sensation of the adverse effects being much impressive than the positive effects obtained, soon all the hopes placed on Koch's remedy seemed to vanish (Ross 19--?). In 1891, a report was issued commenting the 55 trials undergone in Prussia between last 1890 and early 1891. This report, published in the *Klinisches Jahrbuch*, registered about 20% of patients getting better with the treatment and, in summary, more deaths than positive results.

T was discredited as fast as Koch's reputation, even if the political-social-personal context that surrounded him played an important role in that (Ross 19--?; Sahli 1912; Daniel 1997; Gradmann 2001). Koch intended to be eximed of his academic duties to develop and sell the tuberculin, but the Prussian Government seemed to have other plans for him: to rule an Institute able to compete the Pasteur's French one, as the two empires were rivals. Koch competed directly with von Behring, a disciple of him which had success selling antitoxins against diphtheria and tetanus and could replace him as director of the Hygiene Institute. Von Behring and Ehrlich (the last by collaborating with Hoetsch) worked with biotechnological companies, as was in vogue among the eminent scientists (also for representing a good income of money). Koch also needed the money of selling his remedy to pay his former wife to get a divorce from her, as he fell in love with a young girl (Hedwig

Freiberg) and wanted to marry her. After the report of the Prussian Government was fully published, in April 1891, tuberculin was discredited and Koch, pushed by the Government, renounced to receive any economical compensation and accepted to be proposed for directing the new institute (Gradmann 2001; Cardona 2007).

2.2 New Tuberculins and other similar products

The first attempt to avoid the reactions was to produce new tuberculins and similar products, a thing that Koch did himself, all of them being obtained from tubercle products and differing in the manufacture and/or the excipients. The Old Tuberculin, as was commonly called the original Koch's remedy, was based on human tubercle cultures grown on nutrient broth with a 5% of glycerin, sterilised by steam, evaporated, filtered and adding a 0,5% of phenol to be further refiltered. The New Tuberculin and the Koch's bacilli emulsion were the newest products developed by Koch, intending to ameliorate the first version of tuberculin. To generate the New Tuberculin, the steamed cultures were ground and mixed with glycerin to obtain only the insoluble parts of bacillary bodies, and it was developed in 1897. The Koch's bacilli emulsion was from 1901, and was based on powdered tubercle culture suspended in a mixture of half part of glycerin and half of distilled water, in order to obtain an emulsion.

Many other tuberculins were designed, generally classified in exotoxins or soluble products (mere filtered extracts of tubercle bacilli), endotoxins (containing the less soluble substance of microorganisms, also differing according to the process of extraction), and a third group, including both products, the soluble and insoluble (Wilkinson 1909; Riviere and Morland 1913). Some authors considered the albumose to be responsible for the reactions, thus albumose-free tuberculin from cultures grown in albumose-free medium were generated. Beraneck tuberculin was one of this, based on a mixture of filtered culture of tubercle bacilli grown in albumose-free medium plus an extract of bacillary bodies in 1% of phosphoric acid (Riviere and Morland 1913). Wolff-Eisner refined the Koch's New Tuberculin by filtering the powdered body-substance of tubercle bacilli through a Berkefeld candle to substract all fragments of bacilli (Sahli 1912). The products differed in the way they were obtained and treated, thus how the cultures were killed (by mechanical, physical or chemical means), how and how much they were filtrated, how they were dissolved and how and with what they were treated after.

New tuberculins appeared all over the world: Hunter's modification B, von Ruck's Watery Extract, Behring's TC, and many others (Trudeau 1907). With the promise of avoiding reactions also other products were commercialized, as the Partigens of Much of Hamburg. Even if they weren't considered as tuberculins, they could in fact be so-called, as were supposed to be partial antigens of *M.tuberculosis* bacilli extracted from the non-soluble part of the cultures, further treated by alcohol and ether to obtain them (Rothschild 1921).

Friedmann thought the reactions could be avoided if using cultures of other Mycobacteria, and developed a vaccine from *M.chelonei* cultures. He gave it therapeutically with success, but he failed in obtaining reactionless vaccination. However, he even went further, proving the vaccine to be quite useful if given post-exposure in selected cases and prophylactically (Belmes 1937; Vilaplana and Cardona 2010).

Even the Medical Research Council (MRC) had its own tuberculin, supposedly better than other candidates, they finally had to admit in 1924 it was not better than other products (Bryder 1988).

At the end, the best definition for tuberculin seems to be the one given by Pottenger: all products made from tubercle bacilli which contain their bacterial proteins (Pottenger 1913).

Some products produced more local reactions, mostly by a depôt effect, as did the Koch's Bacillary Emulsion and the New Tuberculin, as remained as insoluble deposit at the site of the injection for more time. The more soluble tuberculins, on the other hand, were supposed to generate more general reactions (Riviere and Morland 1913).

The main problem of the products was its preparation, as they all required dilutions and these were performed by the physicians themselves, a fact that the manufacturer of the Beraneck tuberculin improved (as its dilutions could be already provided) ensuring a better uniformity of concentration (Sahli 1912). The concentration was important to graduate the doses of the vaccines, and this was indispensable to be able to organize to time the injections (Wright 1902).



Fig. 1. Partigens of Deycke-Much.

The Old Tuberculin begun to be considered as the best for a diagnostic use. However, as pointed out Sahli, the therapeutic value of the treatment with different tuberculins were not comparable, as no standard existed (Sahli 1912).

Sahli also wrote that good responses could be obtained with all the products available if the right technique was used, but unfortunately, irrespective of which 'new' tuberculin was used, the reactions appeared to be similar, though varying somewhat in intensity (Sahli 1912).

The Partigens were tuberculin products, supposed to achieve good outcomes with less reactions, for being partial antigens instead of the former tuberculins. The Partigens were obtained from the insoluble parts of *M.tuberculosis* cultures after treating them with alcohol and ether, to obtain the 3 partial antigens: the fatty-acid-lipoids (soluble in alcohol); the neutral and highly molecular fats (soluble in ether) and the non-soluble residuum, supposed to belong to the group of proteins (Rothschild 1921). The picture shows how the Partigens were commercialized, providing diluted concentrations for better adjust the doses.

3. Dosage schedules

3.1 The clue of the dosage

It has already been said that no tuberculin was able to avoid reactions, and the difference between them was the intensity of the adverse effects. As soon as this became evident, the scientists and physicians devoted their efforts to find a safe schedule of inoculations. They were mainly two schools of therapists: those believing in true immunization, and thus only to be obtained by large tuberculin doses; and those believing in the recall of host immunity, and thus easily to be achieved by administering small doses of the remedy (as higher doses could do much harm and the effect of a stimulus is not always proportional to the intensity of the stimulus) (Sahli 1912; Pottenger 1913; Vilaplana and Cardona 2010).

Koch observed he needed high doses to obtain the effects he wanted in tuberculous focus, even if this implied reactions. For after each inoculation, a reaction happened, which was followed by tolerance. Consequently, next dose had to be higher to overcome this tolerance. This dosage method, consisting in small doses gradually incremented in short intervals, was developed by Ehrlich and coworkers on 1891, and was modified by the proposals of Goetsch in 1901 (introducing long treatment) and Petrushky later (proposing interrupted treatment in selected cases) (Vilaplana and Cardona 2010).

3.2 Sir Almroth Wright and the therapeutic vaccination

Back to 1896, Sir Almroth Wright, based on the observation of the agglutination of typhoid bacilli when being in contact with serum of someone's infected but not to someone's not infected, considered this a protective process and decided to use it to distinguish the typhoid fever from the Malta fever. It was known, from about 200 years before, human are able to generate resistance to infections, something already used by Jenner (vaccination with cowpox to prevent smallpox, 1796) and Pasteur (live attenuated bacilli to protect against anthrax, in 1870s) among others. But Wright feared using alive bacteria for this purpose could generate acute disease, and advocated for using dead bacilli instead, as he considered they should generate protective immunity as well (as did Dr. Ferran)(Vilaplana and Cardona 2010). Thus with these ideas he developed the typhoid vaccine to prevent typhoid fever, and demonstrated in vaccinated subjects a higher agglutinin levels similar to the levels found in those individuals who had survived an episode of the disease. Wright

thought that if vaccination could generate protective substances in naïve subjects, it would probably boost the already existing protective substances if administered to infected individuals. From this assumption, he developed his idea of therapeutical vaccination: the vaccines wouldn't only be useful to prevent, but also to heal. With this purpose, he began to use heat-sterilized cultures of staphylococci to treat localized infections of staphylococcal nature. In 1902, he observed the agglutinin levels were decreased in the infected individuals but increased if these subjects were treated with dead bacterial cultures.

Therapeutical vaccinations also lead him to the observation of an immediate aggravation of the patient's condition, what he called the "Negative Phase" (Wright 1902).



Fig. 2. Actual image of the St.Mary's Hospital in London, UK. Wright directed the former Inoculation Department of this hospital, devoted to administer the vaccines therapeutically.

Wright believed the reason for these Negative Phases was the vaccination exhausting the existing protective substances. Once the Negative Phase was overcome, a Positive Phase happened, with an increased well-being and healing tendency, in which the protective

substances hypothetically increased and further decreased, but remaining in a certain amount of residual levels (Cope 1966). He also attributed the intensity of both phases to a problem of dosage, and established a general basis to treat localized infection with bacterial vaccines. If the dose was too low, the Negative Phase diminished, but the Positive Phase could not appear; if it was too high, the Negative Phase was too long, the Positive Phase appearing too late or not appear at all (Wright 1903). In two cases he treated of staphylococchia, he observed a considerable inflammatory swelling in the site of infection. He soon found a relationship between this reaction and the one described by the physicians when using Koch's tubercle vaccine. He also gave an explanation for this: he considered the infectious focus to be broken up, and he warned: if the patient is in a Negative Phase the tubercle bacilli are spread, being able to originate new infectious foci. He considered this to be because a bad-regulated dosage, and propose the rule for any therapeutical vaccination: to consider the resistance ability of both the invading microorganism and the host at the time of inoculation, to well-graduate the doses of the vaccine, timing the injections for any patient in a Negative Phase to be recovered (Wright 1902). Wright believed Koch's reactions were due to an accumulation of Negative Phases, while the true objective was to achieve successive Positive Phases to increase the immunity, thus introduced a new dosage method of tuberculin, based on the inoculation of small doses at spaced intervals (Gunter 1928), giving tuberculin in a 1000 times lower doses than in Koch's time (Riviere and Morland 1913).

3.3 Dosage schedules

In spite of the early discredit which tarnish the usefulness of tuberculin remedy, and even if the history has erased any trace of it, the fact is that its use was increased after Wright's contribution, all over Europe and even America. As previously pointed by Sahli, Pottenger also remarked the difference in the effect between the tuberculins was more quantitative than qualitative (Sahli 1912) (Pottenger 1913).

The administration regimens soon derived to only two (with variations). As after an inoculation tolerance came, only two things could be done: to give a higher next dose to overcome the tolerance or to wait the tolerance to pass. To give a higher next dose implied giving increasing doses at small intervals, and is linkable to Koch's idea of treatment administration. This method was widely used in Europe and America, and seems to be the best one to treat phtisical forms of the disease.

Wright's method instead, intended to avoid tolerance, and implied the inoculation of constant small doses administered at long intervals. This method seems to have achieved more positive outcomes in disseminated tuberculosis, local tuberculosis, surface tuberculosis (typical of childhood), and especially if combined with surgery (Wright and Reid 1906; Vilaplana and Cardona 2010).

It is true that reactions continued to happen and scientists gave different explanations for this. Some believed a synergy existed between toxins contained in tuberculin and the toxins already existing in the infected body. There was a "difference theory", believing in the presence of antitoxins in the host, able to balance the disease, which effect could be overcome by the tuberculin administrated. Other theories more concrete believed in a direct effect of the remedy on the leucocytes or the fixation ability of the complement, the lysis of

tuberculin into small toxins (Wolff-Eisner theory), antibody mediated allergy (Von Pirquet) and Hypersensitiveness (Sahli 1912; Vilaplana and Cardona 2009; Vilaplana and Cardona 2010).

But it is also described in literature the most important thing to avoid serious reactions was the ability of the physician to know when and which dose to apply to every single patient, depending on his condition.

Autopsies on fatal cases after administering tuberculin revealed the disease was that bad that no hope of cure or even improvement could be expected, no matter the remedy would have been given (Ross 19--?).

Physicians developed the sense to administer the remedy empirically without having many fatal results, and they had tools to do it.

No inoculation should be repeated before the fever to pass, according to the physicians' recommendation. The worst toxic effects were the cardiac toxic effect, with increase of the blood pressure and albuminuria, thus it is understandable that cardiac complications were among the contraindications of administering the remedy. Other contraindications were great loss of strenght, amyloid or other degeneration tissue, albuminuria and urea (Ross 19--?).

As appointed by Sahli, tuberculin seemed to not have any direct healing power, but enhancing in some way the host immune response. Healthy animals tolerated large doses which would be toxic and even fatal in tuberculous animals and humans. But either in healthy and tuberculous individuals, the tolerance could be increased up to a million times by gradual increase of dose (Sahli 1912).

As explained before, any inoculation of tuberculin was characterized by a local reaction in the site of injection (painfulness, inflammation and sometimes a little uneasiness at the site of injection), a focal reaction at the site of tubercular disease (haemoptysis, pleuritic pains, swelling of tuberculous glands, cough) and a general disturbance (basically fever and pain, loss of appetite and depression); but also to be followed by an immunizing response: with an improvement of tuberculosis symptomatology, a believed increase of the antibody content in the blood and a decrease on the response to the injected tuberculin (Riviere and Morland 1913). As it was no way to predict the effect (either good or bad) of the remedy on the infectious focus, physicians had to be guided by the effects on the symptomatology to infer the amount of the effect produced by a dose of tuberculin (Riviere and Morland 1913). The optimum therapeutic dose was the maximum amount of tuberculin which could be tolerated at any particular moment without producing any severe effects, and depended of each individual, as high interindividual variability existed (Sahli 1912).

Thus physicians used dosage tables to be helped to choose the right doses. They worked with 10% dilutions, beginning at 10000, the remedy given intradermically or subcutaneously. The most common schedule implied administering tuberculin once a week (twice a week at the most), during a minimum of a fortnight. The administration was adjusted according to the tolerance appeared, but being treated in public services or private practices also influenced this point. First, the physicians themselves prepared their tuberculins, but soon some pharmacists begun to produce and sell them at every point worldwide. Some of the products were sold as syringes with already prepared dilutions,

which increased the uniformity of the preparation (Pottenger 1913) and avoided the variations in concentration of the active principle (Sahli 1912).

The physicians recommended the treatment and patients themselves bought the remedy to be administered, and even if it was cheap compared to other treatment, it still was expensive for the poor, which were the population collective more susceptible to need it (Salvat-Papasseit 2007).

"Tuberculin is quite harmless, if there is no tuberculosis". Wilkinson

"Tuberculin is not a poison". Pottenger

"The best rule to follow: better too little than too much tuberculin!". Sahli

"The physician of the future will, I foresee, take upon himself the rôle of an immunizator". Wright

Fig. 3. Quotes on tuberculin treatment, published in the manuscripts of that time.

4. Tuberculin and its historical context

4.1 Tuberculin's use

The scientists of that time tried to stick to every treatment which seemed to give any hope to the tuberculous patients, with the basic knowledge on medicine and immunology then available. Wright invented the use of the Opsonic Index as a biomarker for predicting good responses in tuberculin treatment (Wright and Douglas 1903-1904; Wright and Reid 1906; Ogilvy 1908), which years after revealed to be non-specific (Riviere 1914; Cope 1966) and brought the idea of "Autoinoculation". Wright called the Autoinoculation to some disturbance of the site of the disease, which supposedly generated a continuous periodic escape of bacilli or bacillary toxins to the blood stream, causing bursts of clinical symptoms as any chronic disease with acute episodes would do (Wright and Reid 1906). As the balance between the host response and the virulence of the infection would be the most important fact in the way the disease would develop, while certain amount of antigen was believed to be constantly needed to immunize, its excess could fatally overpower the host response. The source of antigens needed to maintain this residual host response needed could be provided by the infectious focus itself or externally, by inoculation of tuberculin (Riviere 1926), while rest would contribute to heal the infectious foci (Canetti 1955). English sanatoria, following this idea, combined resting hours with working hours at the fresh air, as part of the therapy (Bryder 1988).

Thus tuberculin treatment was administered combined to the hygienic measures commonly prescribed at that time: rest (which would favor the healing), fresh air and an improvement of nutrition (which would favor the immune system). At that time, sanatoria had flourished all over Europe and even America, and people with means attended them to be cured of tuberculosis or at least improve their hampered health status. On 1912, more than 200 institutions in UK and the 70% of the German ones used tuberculin as a standard regimen (Riviere and Morland 1913).

But sanatoria were expensive, and even if no one was safe of suffering tuberculosis, the truth is that the poor got the worst part. They lived in small overcrowded and poor-ventilated apartments in the cities, which favored the spread of the infection, and they were

malnourished, which implied immunosuppression. Charity sanatoria appeared in United Kingdom to cope with this big problem for public health, in order to both diminish the tremendous effect on the country's economy and to isolate the infectious sources (Bryder 1988). At 1921, the UK decided the remedy to be cofinanced depending on each family situation, but this measure had to be abandoned because it revealed to be non sustainable. Notes on 1937 already denounced the beneficence giving more money to cancer research to tuberculosis, as the last was considered a disease of the poor (Bryder 1988).

In 1912 it cost between 6,5 pences and 8 shillings depending on the tuberculin used (at that time, one pound was divided in 20 shillings, and each shilling into 12 pence), thus tuberculin was a cheap remedy (Riviere and Morland 1913). Receiving the treatment at non-charity sanatoria highly increased the cost of the remedy from a total of 2£ up to 32£ for the medical constant supervision, and other costs had to be added to this amount (the stay, food, etc) (Wilkinson 1909).

But the poor also had another problem: they couldn't lose their jobs, thus they didn't attend the charity sanatoria neither. With the aim of helping them considering this problem of them, Sir Robert Philip opened the Victoria Dispensary for Consumption and Diseases of the Chest in Edinburgh. Similar dispensaries appeared worldwide: in the period from 1912 and 1917 about 400 dispensaries existed in UK, 450 in America and 600 in Germany (Riviere 1926). Dispensaries were important not only because they permitted the patients to attend their jobs while being treated with tuberculin (Wilkinson 1909), but because the personnel taught the people to measure their temperature and basic guidelines on hygiene to improve their health status. Camac Wilkinson left a book devoted to these dispensaries, thoroughly describing his work at his Dispensary for the Poors in the Kennington Road of London. Besides administering tuberculin treatment and following-up the patients, the physicians in the dispensaries did screening and surveillance of contacts conducting epidemiological studies of undeniable value (Wilkinson 1909; Vilaplana and Cardona 2010). Tuberculin therapy continued to be used worldwide until the appearance of chemotherapy, when it was abandoned. Its efficacy being variable on the skills of each physician people feared the dangers of the reactions following its administration. However, a review of ancient documents provides an objective impression of the usefulness of the remedy: it was used for more than 50 years with more successes than failures, and thus even if it could be improved, it worked (Vilaplana and Cardona 2010).

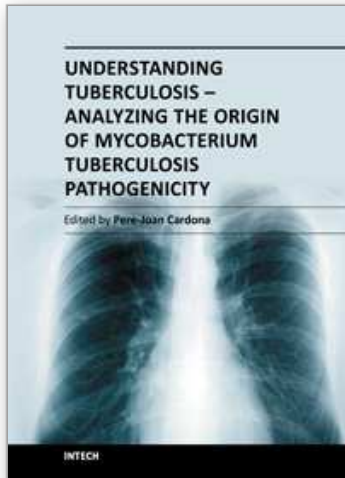
The recent past years, research on tuberculosis has been focused on designing and developing new vaccines, mainly to be used prophylactically, but also therapeutic and to be given postexposure (Beresford and Sadoff 2010). The candidates are based on single antigens of Mycobacteria, obtained from cultures or by recombinant processes, or in whole organisms comminuted and/or sterilized, thus they could be considered as tuberculins. Several candidates are in the pipeline for being used as immunotherapy, thus to be administered to a person once being exposed to the tubercle bacilli to prevent reactivation or progression to active tuberculosis, or to shorten or improve the response to chemotherapy (2009). Used as immunotherapy, all vaccines generate local reactions which intensity depends on the candidate (Johnson, Kamya et al. 2000; Sander, Pathan et al. 2009) (Vilaplana, Montané et al. 2010), and they could all be considered the local reactions described by Koch. No fatal reactions are encountered, but this could be due to the fact that nowadays infection can be easily discriminated from active disease by X ray assay, thus

patients can be carefully selected, something non even envisageable at Koch's time. Moreover, nowadays we can follow-up the patients tightly, controlling general reactions and screening serious focal reactions with imaging. So should we fear that much Koch's reaction up to the point of avoiding using vaccines therapeutically? Probably not, especially if we do consider Wright's recommendation of sterilizing as much as possible the infectious foci before administering the vaccines (Wright 1904), something now possible with the help of chemotherapy, actually an advantage that some candidates have already used as a therapeutic strategy with success (Johnson, Kamya et al. 2000; Vilaplana, Montané et al. 2010).

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Mycobacterium tuberculosis in an attempt to understand the extent to which the bacilli has adapted itself to the host and to its final target. On the other hand, there is a section in which other specialists discuss how to manipulate this immune response to obtain innovative prophylactic and therapeutic approaches to truncate the intimal co-evolution between Mycobacterium tuberculosis and the Homo sapiens.

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